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Researches in the Quinazoline Group

DISSERTATION

SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN THE FACULTY OF PURE SCIENCE OF COLUMBIA UNIVERSITY.

BY

GEORGE AUGUSTUS GEIGER, A.B., A.M.,

NEW YORK CITY

1911

EASTON, PA.:
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TO MY PARENTS.

ACKNOWLEDGMENT.

An opportunity is given here for the author to express his sincere thanks to Professor Marston Taylor Bogert for the suggestions which led to a successful completion of the following investigations. Without his guiding hand the opening of these fields would have been fraught with great difficulty. The author also wishes to state his appreciation for the courtesies extended to him by Doctor J. M. Nelson and Mr. H. L. Fisher and fellow workers in the laboratory.

ORGANIC CHEMISTRY LABORATORY,
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GEORGE A. GEIGER.

GENERAL INTRODUCTION.

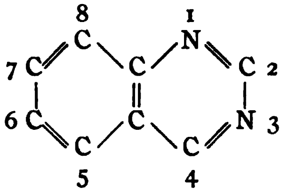
On surveying the work which is to be described in the following pages, it appeared that the various compounds dealt with fall logically into three groups. Consequently, it has seemed best to divide the subject as follows:

I. This division will contain short descriptions of the simpler quinazolones* previously prepared and a more lengthy description of those which we believe to be new. These quinazolones, in general, are the parent substances of those described in II and III.

II. Under this division will be considered the quinazolone iodalkylates which resulted from adding alkyl iodides to the quinazolones of I.

III. Finally, in division III will be found the nitroquinazolones obtained by nitration of some of the quinazolones of I and the amino derivatives obtained by reduction of these nitroquinazolones.

In naming the compounds so obtained, the order of numbering of the different positions on the quinazoline cycle is shown by the structural formula:



I.

THE SIMPLER QUINAZOLONES.

INTRODUCTION.

4-Quinazolone and 3-N Derivatives.

By heating carboxycyanamidobenzoyl with water Peter Griess[1] obtained a compound which he called carbimidamidobenzoyl which melted at 214° C. This compound is identical with 4-quinazolone.

---

*The shorter term "quinazolone" has been substituted throughout for "4-ketohydroquinazoline."

Weddige[2] fused orthoamidobenzamide with formic acid and the formyl derivative resulting, when heated, split off water, giving the 4-quinazolone. The melting point is given as 209° C.

Some time after, Bischler and Burkart[3] prepared 4-quinazolone by heating the ammonium salt of formylorthoamidobenzoic acid. They give the melting point as 209° C.

Niementowski,[4] by fusing formamide and anthranilic acid at 120°–130° C. for three hours, obtained a white product which melted at 212° C.

In working with the 4-quinazolone Knape[5] prepared the 3-N methyl by dissolving it in methyl alcohol with caustic potash and adding methyl iodide. After standing awhile in the cold, a fine white crystalline product fell which melted at 71° C.

In an analogous manner, using propyl and butyl iodides, Bogert and May[6] made the 3-propyl and 3-butyl-4-quinazolones which melted at 82° C. and 73° C., respectively.

The 3-phenyl-4-quinazolone was prepared by Paal and Busch[7] by oxidation of phenyldihydroquinazoline with potassium permanganate. They found that it melted at 219° C. They also obtained 3-paratolyl-4-quinazolone from 3-paratolyldihydroquinazolone in the same manner.

To this list we have added the 3-ethyl and the 3-benzyl-4-quinazolones, as will be described in the experimental part.

2-Methyl-4-quinazolone.

In 1886 Weddige,[2] by heating acetylorthoamidobenzamide, prepared the 2-methyl-4-quinazolone.

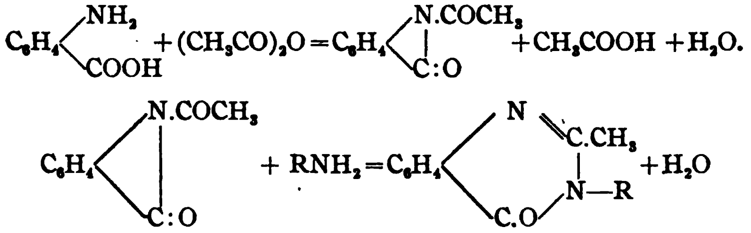
Later Bischler and Burkart[3] heated the ammonium salt of orthoacetaminobenzoic acid and also obtained the 2-methyl-4-quinazolone.

Bischler and Lang[8] found that, when phen-β-methylmiazin was treated with chromic acid, it was oxidized to the 2-methyl-4-quinazolone. They also showed that permanganate would not effect this oxidation.

Acetamide when fused with anthranilic acid, according to Niementowski,[4] gave a 50 per cent. yield of the 2-methyl derivative.

By heating anthranilicnitrile and acetic anhydride in a sealed tube, Bogert and Hand[9] obtained the same compound as the above.

It remained for Anschütz, Schmidt, and Greiffenberg[10] to develop the reaction which has proved to be very useful and fertile in preparing a large number of quinazolones. When anthranilic acid is boiled down with an excess of acetic anhydride, acetanthranil crystallizes out. This anthranil can then be condensed with any primary amine to form quinazolones. The reaction may be represented as follows:



As to the higher homologues, they may be prepared according to the general reactions just given, using the anhydride with the next higher carbon content.

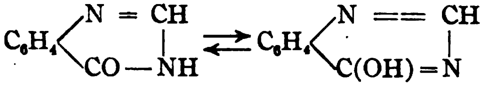
By making use of Anschütz, Schmidt, and Greiffenberg's reaction, we have prepared 2-methyl-3-paratolyl-4-quinazolone, 2-methyl-3-paranitrophenyl-4-quinazolone, 2-methyl-3-α-naphthyl-4-quinazolone, and 2-methyl-3-β-naphthyl-4-quinazolone, none of which have been previously prepared to the best of our knowledge, although both α and β-naphthylamines have been condensed with anthranils carrying some group on the benzol nucleus, such as amino and nitro groups.

Experimental Part.

As has already been stated, it has become necessary to describe in this division a number of quinazolones previously prepared, owing to the fact that they were the mother substances of all which follow in Divisions II and III.

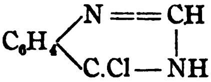
Lengthy descriptions of these quinazolones have been omitted, but the reference to the original article is generally given.

4-Quinazolone,



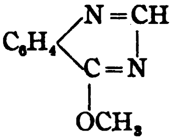
.——Niementowski's[4] method of fusing anthranilic acid with formamide was followed. If the anthranilic acid was crude, boneblacking was necessary to obtain a pure product. For large amounts alcohol was used as a crystallizing medium. Melting point, 212° C. as found by Niementowski.

4-Chlorquinazoline,



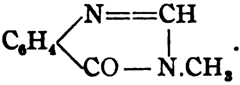
.—This compound was prepared by Gabriel's[11] method with the modification given by Bogert and May.[6] After two or three trials the chlorquinazoline was obtained in a fair state of purity and dried *in vacuo*. Melting point 96° C.

4-Methoxyquinazoline,



.—Bogert and May[6] give the process which was used. Fresh absolute methyl alcohol was found to be essential. 15 grams of the chlorquinazoline give 8 grams of the methoxyquinazoline. Melting point 35°–36° C.

3-Methyl-4-quinazolone,



.—On the first trial Knape's[5] method was followed. The crystals which separated were contaminated with potassium iodide, and, in order to get rid of this, the entire crystals were treated with chloroform and filtered; but it was found that nearly all the chloroform had to be evaporated before crystallization commenced and then an almost solid mass was obtained which melted at 105° C. instead of 71° C., as given by Knape.

We found a method which, in our opinion, is a decided improvement and explains the discrepancy in the melting points. When the quinazolone is dissolved in methyl alcohol with caustic potash and methyl iodide, and allowed to stand, crystallization sets in about 1¹/₂ to 2 hours after commencing the operation. The crystals thus obtained were filtered by suction and, instead of using chloroform, they were added to cold water. Solution of the whole was immediately effected, but after standing about fifteen minutes, white, small, feathery crystals began to appear until the beaker contained a semi-solid mass. These were filtered and recrystallized from hot water, in which they were very soluble, while almost insoluble in cold water. After drying in the air for four days a melting point of 70° C. was found which was very close to Knape's figure. A portion was then placed in a vacuum over sulphuric acid for a week and the melting point was then found to be 105° C. which agrees with our first figure. Consequently good figures for one molecule of water of crystallization were obtained.

Dried *in vacuo* four days, then heated to 80° C. for 1 hour, and again dried *in vacuo* for 1 hour, the following figures were obtained:

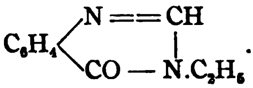
0.2009 gram of air dried substance lost 0.0201 gram when dried as described above.

	Calculated for $C_9H_8N_2OH_2O$. Per cent.	Found. Per cent.
H_2O	10.11	10.00

A Dumas nitrogen on the anhydrous substance proved that it was the 3-methyl-4-quinazolone.

0.1031 gram of substance gave 15.7 cc. of nitrogen at 767 mm. and 23° C.

	Calculated for $C_9H_8N_2O$. Per cent.	Found. Per cent.
Nitrogen*	17.50	17.32

3-Ethyl-4-quinazolone,  $C_6H_4\Big\langle\begin{matrix}N == CH\\ \quad\quad|\\ CO - N.C_2H_5\end{matrix}$.—After several unsuccessful attempts the above compound was prepared as follows: 20 grams of 4-quinazolone were placed in a flask and enough ethyl alcohol added to form a thick paste. 7.6 grams of stick caustic potash were then added and the flask shaken until all the quinazolone had gone into solution. After pouring in 21 grams of ethyl iodide, the solution was boiled under a reflux until a piece of litmus paper, which had been added, turned red. About three-quarters of an hour gentle boiling was necessary, during which crystals of potassium iodide separated. Having distilled off the alcohol, a semi-crystalline and oily, viscous residue remained in the flask. This completely dissolved in about 100 cc. of water. (At this point in a previous trial, this water solution was subjected to steam distillation, but nothing was recovered from the distillate.) The water solution was poured into a separatory funnel and extracted with a large volume of ether. After the first extraction salt was added, and the extraction was repeated two or three times. The salting materially aids the removal of the quinazolone. The combined ether extracts were dried over dry potassium carbonate which gave a clear colorless solution after filtering, whereas calcium chloride invariably left a yellow color. On evaporating the ether, aborescent film-like crystals separated above the surface of the liquid, giving a frost-like appearance to the flask; at other times they appeared to radiate from a common center. After all the ether had evaporated, a solid mass of crystals was obtained; in several trials, however, only an oil remained which, when poured into a beaker, solidified with the evolution of considerable heat. The whole mass was then crystallized by dissolving in boiling ether and subsequently setting the beaker in an ice pack. By this treatment fair-sized, thick needles were obtained, white in color, which melt at 102° C. (cor.). The yield was 13 grams which is 54 per cent. of the theory. This 3-ethyl-4-quinazolone was found to be soluble in cold water, cold ethyl alcohol, hot acetone, and hot benzol, but on cooling, forms a milky solution in the last-named solvent.

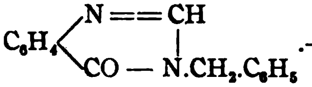
---

*All nitrogen determinations were conducted according to the Dumas method.

The product from the ether extraction may also be purified by vacuum distillation but the delivery tube must be surrounded by hot water. The quinazolone distils at 182° C. under 15 mm. pressure, in clear oily drops which crystallize on cooling. The thermometer in the oil registered 216° C.

0.1002 gram of substance gave 14.4 cc. of nitrogen at 754 mm. and 23° C.

	Calculated for $C_{10}H_{10}N_2O$. Per cent.	Found. Per cent.
Nitrogen	16.09	16.06

3-Benzyl-4-quinazolone, 

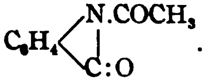
$$C_6H_4\left\langle\begin{array}{l}N == CH \\ \quad\quad\;\; | \\ CO - N.CH_2.C_6H_5\end{array}\right.$$

.—Having added enough methyl alcohol to 10 grams of 4-quinazolone to form a thick paste, 4 grams of caustic potash were introduced and the flask shaken until solution was complete. After adding 8 grams of benzyl chloride, the solution was boiled under a reflux condenser on a water bath. In about one-half hour potassium chloride began to separate, and, about fifteen minutes later, so large an amount had separated that violent bumping ensued. The potassium chloride was filtered off while the solution was still hot. In the filtrate, after slight cooling, white needles were deposited. These were filtered by suction until dry and boiled with hot water, in which they were insoluble, to remove any adhering potassium chloride. They crystallized from a mixture of methyl alcohol and water in long, white needles. This compound was also insoluble in cold chloroform, acetone, ether, benzol and ethyl alcohol; soluble in hot chloroform, benzol, acetone and ethyl alcohol. The yield was 6 grams. The perfectly dry white crystals melted at 116° C. (cor.).

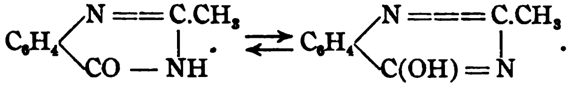
0.1003 gram of substance gave 10.9 cc. of nitrogen at 744 mm. and 23° C.

0.1884 gram of substance gave 0.5236 gram of CO_2 and 0.0818 gram of H_2O.

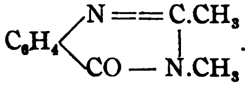
	Calculated for $C_{15}H_{12}N_2O$. Per cent.	Found. Per cent.
Nitrogen	11.86	11.98
Carbon	76.27	76.08
Hydrogen	5.08	4.82

Acetanthranil, 
$C_6H_4<\begin{matrix}N.COCH_3\\ |\\ C:O\end{matrix}$.—When anthranilic acid is added to twice its weight of acetic anhydride and boiled down, the acetanthranil crystallizes on cooling. Filtered, plated and dried, it melts at 80° C. From technical anthranilic acid the yield is very poor, averaging about 40 per cent. of the theory because recrystallization is necessary.

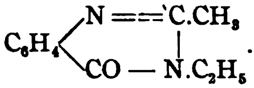
2-Methyl-4-quinazolone,

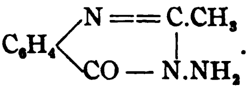

$$C_6H_4<\begin{matrix}N=\!=\!=C.CH_3\\ \qquad\quad |\\ CO-NH\end{matrix}.\rightleftarrows C_6H_4<\begin{matrix}N=\!=\!=\!=C.CH_3\\ \qquad\qquad |\\ C(OH)=N\end{matrix}.$$

—This was prepared by the method of Anschütz, Schmidt, and Greiffenberg.[10] It was noted in some cases that, where a large amount of quinazolone was made, complete condensation did not take place but that the amide of acetanthranilic acid was obtained. Melting point 170° C. By boiling with dilute KOH the 2-methyl-4-quinazolone was obtained melting at 235° C. (uncor.).

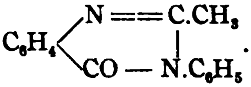
2,3-Dimethyl-4-quinazolone, 
$C_6H_4<\begin{matrix}N=\!=\!=C.CH_3\\ \qquad\quad |\\ CO-N.CH_3\end{matrix}$.—This was conveniently prepared by adding acetanthranil to an excess of 10 per cent. solution of methylamine. The quinazolone crystallizes from hot water in long, white needles which melted at 72° C. (hydrous) and at 111° C. (anhydrous) (cor.).

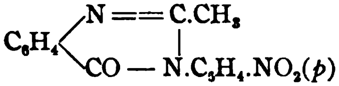
Methylation of the 2-methyl-4-quinazolone was also tried as performed by Bogert and Gotthelf.[12] The first method, however, is more convenient and the yield is better.

2-Methyl-3-ethyl-4-quinazolone, 
$C_6H_4<\begin{matrix}N=\!=\!=C.CH_3\\ \qquad\quad |\\ CO-N.C_2H_5\end{matrix}$. —Prepared in an analogous manner to the above by adding acetanthranil to a 10 per cent. solution of ethylamine. It crystallizes from hot water in long, white needles melting (anhydrous) at 67° C. (cor.).

2-Methyl-3-amino-4-quinazolone, 
$C_6H_4<\begin{matrix}N=\!=\!=C.CH_3\\ \qquad\quad |\\ CO-N.NH_2\end{matrix}$.—

Bogert and Gortner[13] prepared this quinazolone from acetanthranil and an aqueous solution of hydrazine hydrate. It crystallizes with one molecule of water of crystallization from water. It loses this at 100° C. and then melts at 152° C.

2-Methyl-3-phenyl-4-quinazolone,

$$C_6H_4\begin{array}{l}\diagup N = C.CH_3 \\ \qquad\quad\ | \\ \diagdown CO - N.C_6H_5\end{array}$$
.—By heating aniline and acetanthranil together Anschütz, Schmidt, and Greiffenberg[10] obtained this quinazolone. It crystallizes from dilute alcohol in small plates melting at 147° C. (cor.).

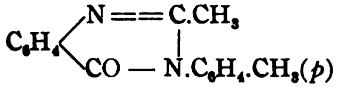
2-Methyl-3-p-nitrophenyl-4-quinazolone,

$$C_6H_4\begin{array}{l}\diagup N = C.CH_3 \\ \qquad\quad\ | \\ \diagdown CO - N.C_3H_4.NO_2(p)\end{array}$$
.—Four grams of dry acetanthranil were ground up with 3 grams of *p*-nitraniline and heated in a test tube at 180° (oil bath) for three-quarters of an hour. A gummy melt was obtained which solidified to a hard dark mass on cooling. It was again warmed until liquid and poured into cold ethyl alcohol. On warming the alcohol, it all dissolved and yellow leaflets were deposited after cooling. After recrystallization from ethyl alcohol it melted sharply at 193° C. (cor.). Yield was 2 grams.

0.1020 gram of substance give 13.5 cc. of nitrogen at 755 mm. and 20° C.

0.2020 gram of substance gave 0.0729 gram of water and 0.4728 gram of carbon dioxide.

	Calculated for $C_{15}H_{11}N_3O_3$. Per cent.	Found. Per cent.
Nitrogen	14.94	15.04
Carbon	64.05	63.81
Hydrogen	3.91	4.00

It was thought that metanitraniline would condense just as readily as the para but on trial we were unable to effect the condensation.

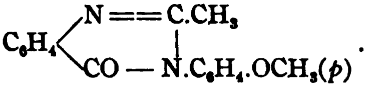
2-Methyl-3-p-tolyl-4-quinazolone,

$$C_6H_4\begin{array}{l}\diagup N = C.CH_3 \\ \qquad\quad\ | \\ \diagdown CO - N.C_6H_4.CH_3(p)\end{array}$$
.—Ten grams of dry acetanthranil

were mixed in a mortar with 7 grams of *p*-toluidine. As the trituration proceeded, the mass became lumped and slightly moist. It was placed in a test tube in an oil bath and began to melt about 80° C. At 100° an evolution of steam commenced and, above this, the temperature had to be raised very slowly and gradually otherwise a violent boiling ensued. When 135° was reached the temperature was allowed to remain there one-half hour longer. The hot liquid melt was poured into alcohol in which it dissolved. As nothing separated on cooling, about one-half volume of water was added when fine, greenish crystals separated. Recrystallized from a mixture of alcohol and water long slender crystals were obtained of a grayish white color melting at 151° C. (cor.). It is soluble in cold benzol, acetone, chloroform, methyl alcohol, partly soluble in ether. The yield was 10 grams or about 66 per cent. of the theory.

0.1000 gram of substance give 10.2 cc. of nitrogen at 756 mm. and 24° C.

	Calculated for $C_{16}H_{14}N_2O$. Per cent.	Found. Per cent.
Nitrogen	11.20	11.37

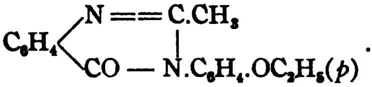
2-Methyl-3-p-anisyl-4-quinazolone,



$$C_6H_4\left\langle\begin{array}{l}N = C.CH_3\\ \quad\quad\quad\;|\\ CO - N.C_6H_4.OCH_3(p)\end{array}\right.$$

.—By fusing acetanthranil and *p*-anisdine in a test tube, Bogert and Beal[14] obtained an oil which crystallized from ethyl alcohol in plates melting at 174° C. (cor.).

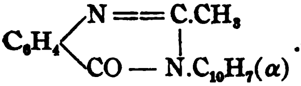
2-Methyl-3-p-phenetyl-4-quinazolone,



$$C_6H_4\left\langle\begin{array}{l}N = C.CH_3\\ \quad\quad\quad\;|\\ CO - N.C_6H_4.OC_2H_5(p)\end{array}\right.$$

.—Bogert and Beal[14] also prepared this from acetanthranil and *p*-phenetidine. It crystallizes from ethyl alcohol in almost white needles, melting at 148° C. (cor.).

2-Methyl-3-α-napkthyl-4-quinazolone,

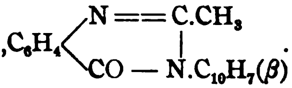


.—When 10 grams of dry acetanthranil were mixed in a mortar with 9 grams of α-naphthylamine, the mass assumed a lumpy, moist appearance. The heating was done in an oil bath and the temperature was gradually raised to 150° C. and kept there for one hour. Water vapor was gradually evolved at this temperature. The resulting dark red oily melt was poured, while warm, in alcohol in which it entirely dissolved. After standing no crystals appeared, but on dilution with water, an oil separated, which became crystalline on standing: further dilution, caused a grayish powder to separate. On crystallization from a mixture of alcohol and water, the product separated in small plates. When filtered it was of a grayish color but soon turns to a purplish red on exposure to the air and possessed an odor resembling naphthylamine, probably due to a slight contamination of the latter. It is soluble in cold acetone, chloroform, benzol and partially soluble in ether. The yield was 10.5 grams. It melted at 136° C. (cor.).

0.1508 gram of substance gave 13.2 cc. of nitrogen at 761 mm. and 24° C.

	Calculated for $C_{18}H_{14}N_2O$. Per cent.	Found. Per cent.
Nitrogen	9.79	9.82

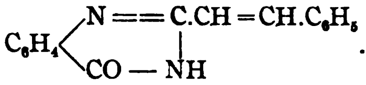
2-Methyl-3-β-naphthyl-4-quinazolone,



—A mixture of 10 grams of dry acetanthranil and 8 grams of β-naphthylamine were heated for about one and a half hours at 140°–160° C. No bubbles of water appeared until 130° C. had been reached and vigorous boiling set in at 140°. The liquid melt was poured directly into ethyl alcohol in which it dissolved. The product crystallized in nodules of short needles. The color of the dry compound is a pinkish red. It is less soluble than the 2-methyl-3-α-naphthyl-4-quinazolone in ethyl alcohol. Nine grams were obtained as a yield. The melting point was found to be 175° C. (cor.).

0.1010 gram of substance gave 8.7 cc. of nitrogen at 772 mm. and 22° C.

	Calculated for $C_{19}H_{14}N_2O$. Per cent.	Found. Per cent.
Nitrogen	9.79	9.91

2-Styryl-4-quinazolone, 

$$C_6H_4\Big\langle\begin{array}{l}N == C.CH = CH.C_6H_5 \\ \qquad\quad | \\ CO - NH\end{array}$$

.—By heating 2-methyl-4-quinazolone with a slight excess of benzaldehyde in a test tube over a flame for about fifteen minutes, Bogert and Beal[15] obtained a melt which crystallized from ethyl alcohol in colorless, silky needles melting at 252°–3° C. (uncor.).

In the same manner the following were prepared, according to Bogert and Beal. Through the kindness of Mr. Beal, we were furnished with some of them.

2-Styryl-3-methyl-4-quinazolone, melting point 170° C. (cor.).

2-Styryl-3-ethyl-4-quinazolone, melting point 124° C. (cor.).

2-Styryl-3-*p*-phenyl-4-quinazolone, melting point 200° C. (cor.).

2-Styryl-3-*p*-tolyl-4-quinazolone, melting point 197° C. (cor.).

2-Styryl-3-*p*-anisyl-4-quinazolone, melting point 223° C. (uncor.).

2-Styryl-3-*p*-phenetyl-4-quinazolone, melting point 204° C. (cor.).

2-Styryl-3-α-naphthyl-4-quinazolone, melting point 187° C. (cor.).

2-*m*-Methoxy-*p*-oxystyryl-4-quinazolone, melting point 280° C. (uncor.).

1-(4-Quinazolonyl)-4-phenyl-1,3-butydiene, melting point 257–8° C.

II.

QUINAZOLONE IODMETHYLATES.

INTRODUCTION.

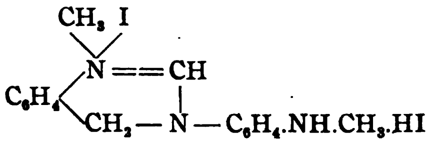
Notwithstanding the fact that, up to this time, a large amount of work has been performed in the quinazoline group, only a few isolated cases are on record of attempts to add an alkyl halide to members of this series.

By heating phenyldihydroquinazoline in a sealed tube at 100° C. with methyl alcohol and methyl iodide, Paal and Busch[7] obtained three products: I. After cooling the contents, crystals, which were probably a periodide, separated; II, from the filtrate from these crystals, they obtained, on standing, a compound of unknown constitution, but which they thought might be an isomer of the following: III, to the mother liquor water was added to turbidity and heated; on cooling, the iodmethylate subsequently crystallized out.

After heating a methyl alcohol solution of the 3-methyl-4-quinazolone in a bomb with methyl iodide, Knape[5] obtained long flat needles which proved to be the iodmethylate. No melting point was given. He also mentions the formation of the quinazolonium hydroxide by the acid of moist silver oxide.

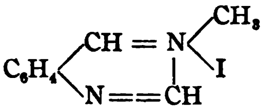
Bischler and Barad[16] treated phen-β-methyl-α-phenylmiazin in a sealed tube with methyl alcohol and an excess of methyl iodide. A liquid resulted which contained crystals of the iodmethylate. An iodethylate was obtained by analogous treatment.

It was found by Paal and Neuburger[17] that when a methyl alcohol solution of metaamidophenyldihydroquinazoline was heated in a sealed tube for twelve hours, it took up two molecules of methyl iodide. They assign the formula



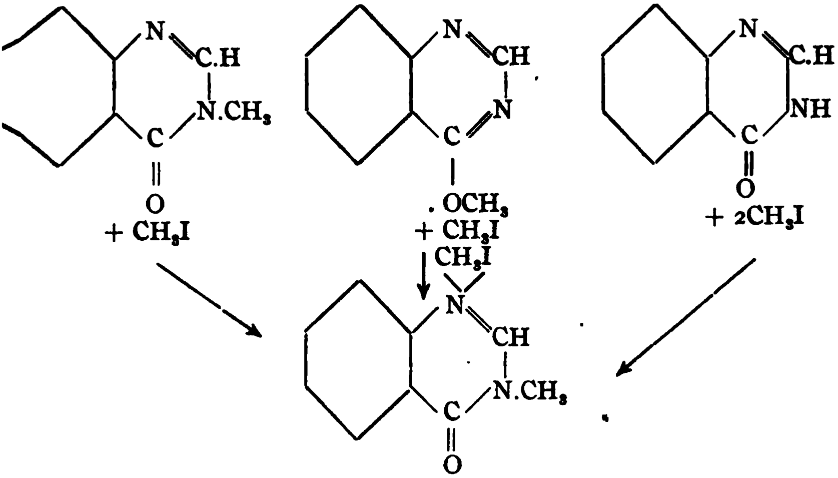
to the product. When this is treated with a caustic soda solution, an oil is obtained which is the iodmethylate itself. It became crystalline on standing.

While investigating quinazoline Gabriel and Colman[18] found that they could obtain the iodmethylate in the cold or much more quickly, by heating in a sealed tube. This gave the quinazolinium hydroxide when treated with potash solution. When the hydroxide was distilled with alkali, they obtained orthoamidobenzalmethylamine. From this fact they assigned the added molecule of methyl iodide to position 3.

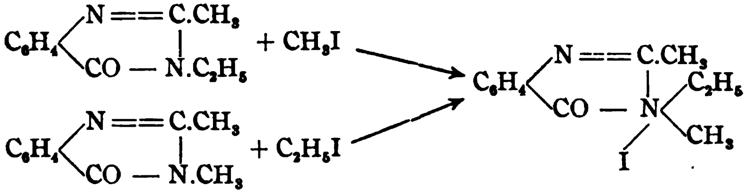


Bogert and May[6] in repeating Knape's[5] method for the preparation of 3-methyl-4-quinazolone found that, if an excess of methyl iodide was present, the iodmethylate of the 3-methyl-4-quinazolone was also formed. Moreover at the same time, they obtained the iodmethylate of 4-methoxyquinazoline, the reaction taking place in the cold before heating. They give the melting point of the 3-methyl-4-quinazolone iodmethylate as 263° C. (cor.) and the 4-methoxyquinazoline iodmethylate as 265° C. (cor.).

On repeating this work we have found these two products were identical, *viz.*, the iodmethylates obtained from 3-methyl-4-quinazolone and 4-methoxyquinazoline. Moreover, when 4-quinazolone is heated with two molecules of methyl iodide, a iodmethylate is obtained which is also the same as the above two. Consequently in case of the 4-methoxyquinazoline a migration of a methyl group takes place; in case of 4-quinazolone, methylation first takes place on the NH-group and then another molecule of methyl iodide adds. The reaction may be represented as follows:



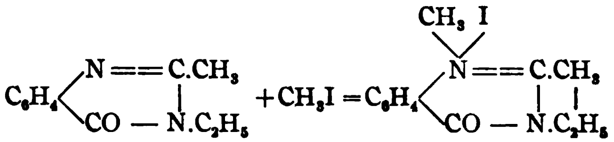
As to the position of the added molecule of methyl iodide, there can now be no doubt that it is added to 1-N. The following facts support this conclusion quite firmly. When methyl iodide is added to 2-methyl-3-ethyl-4-quinazolone a iodmethylate is obtained which melts at 217° C. (uncor.). If ethyl iodide is added to the 2,3-dimethyl-4-quinazolone, the resulting iodethylate melts at 237° C. (uncor.). If in each case, the alkyl halide had added to 3-N, then the same product would have been expected from both, *i. e.*,



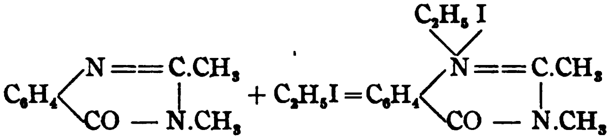
$$C_6H_4\left\langle\begin{array}{l}N = C.CH_3\\ \qquad\ \ |\\ CO - N.C_2H_5\end{array}\right. + CH_3I \longrightarrow C_6H_4\left\langle\begin{array}{l}N = C.CH_3\\ \qquad\ \ |\\ CO - N\left\langle\begin{array}{l}C_2H_5\\ CH_3\end{array}\right.\\ \qquad\ \ I\end{array}\right.$$

$$C_6H_4\left\langle\begin{array}{l}N = C.CH_3\\ \qquad\ \ |\\ CO - N.CH_3\end{array}\right. + C_2H_5I \longrightarrow C_6H_4\left\langle\begin{array}{l}N = C.CH_3\\ \qquad\ \ |\\ CO - N\left\langle\begin{array}{l}C_2H_5\\ CH_3\end{array}\right.\\ \qquad\ \ I\end{array}\right.$$

However, what appears to have taken place is:



$$C_6H_4\left\langle\begin{array}{l}N = C.CH_3\\ \qquad\ \ |\\ CO - N.C_2H_5\end{array}\right. + CH_3I = C_6H_4\left\langle\begin{array}{l}\overset{CH_3\ \ I}{N} = C.CH_3\\ \qquad\ \ |\\ CO - N.C_2H_5\end{array}\right.$$



$$C_6H_4\left\langle\begin{matrix}N == C.CH_3\\ \quad | \\ CO - N.CH_3\end{matrix}\right. + C_2H_5I = C_6H_4\left\langle\begin{matrix}\overset{C_2H_5\ I}{\overset{\vee}{N}} == C.CH_3\\ \quad | \\ CO - N.CH_3\end{matrix}\right.$$

Moreover, 2-methyl-4-quinazolone and 2-styryl-4-quinazolone yield iodmethylates without the —NH-group being methylated first. Consequently it appears reasonable to assume that the alkyl halide would not add to the imino group, the H of which is easily replaced by alkyl radicles, without first having undergone methylation; however, no methylation did take place.

Besides these compounds already mentioned, we have successfully prepared a large number of alkyl halides addition products of the quinazolones, although failures were encountered in a few cases. It was found necessary to use pressure and high temperature, as no addition would take place at low temperature or atmospheric pressure.

The melting point of most of these compounds is characteristic. Just after melting, a violent effervescence is noted while bubbles rapidly ascend in the tube.

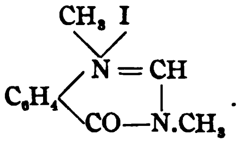
The action of moist silver oxide on these alkyl halide addition products has not been studied in detail, although a few attempts have been made to isolate the products. In case of the 2-methyl-3-alkyl-4-quinazolones we have not been able to isolate the products even on evaporation of the solution. When, however, a large group like the styryl group occupied position 2 we were able to get a product which, however, does not appear to be the quinazolonium hydroxide. These products are described in detail in the experimental part.

Experimental Part.

Before describing any of these addition products, it might be well to state that in order to determine the iodine, it was not necessary to run the halogen estimation by Carius' method. The weighed amount of substance, about 0.2–0.3 gram, was added to about 100 cc. of cold water and heated until dissolved. In case of the few found to be entirely insoluble in hot water enough alcohol to dissolve them completely could be added to the hot water. A solution of silver nitrate containing a small amount of nitric acid was then added and the mixture heated until the silver iodide had settled. This was filtered through a Gooch crucible, dried, and weighed. Excellent results were obtained by this method.

Addition of Methyl Iodide to 4-Methoxyquinazoline.

Bogert and May[6] found that the 4-methoxyquinazoline seems to add when in contact with methyl iodide in the cold but they completed the reaction by heating in a sealed tube. On repeating this work we observed the same results but used methyl alcohol as crystallizing medium instead of water. It crystallizes from this solvent in short thick needles. Bogert and May give 265° C. (cor.) as melting point. We found 270° C. (uncor). When dissolved in methyl alcohol solution and methyl iodide added, no addition took place in the cold after standing five days.

3-Methyl-4-quinazolone Iodmethylate, .— Knape[5] made this derivative by heating a methyl alcohol solution of the 3-methyl-4-quinazolone with methyl iodide in a sealed tube at 100° C. for an hour. This was tried and gave good results. Knape gave no melting point.

It can also be prepared by heating the quinazolone with methyl iodide alone in a sealed tube at 100°. The yield is almost quantitative. It crystallizes from methyl alcohol in short, thick needles. It melts with decomposition 270° C. (uncor.). Bogert and May give 263° C. (cor.).

0.1025 gram of substance gave 8.7 cc. of nitrogen at 770 mm. and 28° C.

0.3001 gram of substance gave 0.2343 gram of silver iodide.

	Calculated for $C_{10}H_{11}N_2OI$. Per cent.	Found. Per cent.
Nitrogen	9.27	9.44
Iodine	42.03	42.19

Addition of Methyl Iodide to 4-Quinazolone.

Three grams of the 4-quinazolone were heated with the calculated amount of methyl iodide at 100° C. for seven hours. There was pressure in the tube, while the caked mass was colored red. It was crystallized from methyl alcohol from which it separated in short, fine, yellowish needles. It is soluble in cold water, partly soluble in ethyl alcohol, insoluble in ether, acetone, and benzol. Melting point 269° C. (uncor.). The yield was about 20 per cent. of the theory.

Another tube was run containing a slight excess of 2 molecules of methyl iodide. The product from the tube possessed a penetrating odor. Crystallized from methyl alcohol and boneblacked, it came out in white needles. It melts at 269° C. with evolution of gas. The yield was about 50 per cent. of the theory.

0.1020 gram of substance gave 8.5 cc. of nitrogen at 763 mm. and 26° C.

0.2050 gram of substance gave 0.1593 gram of silver iodide.

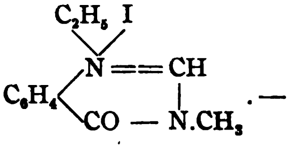
	Calculated for $C_{10}H_{11}N_2OI$. Per cent.	Found. Per cent.
Nitrogen	9.27	9.28
Iodine	42.03	41.99

This product therefore had first undergone methylation before addition of a molecule of methyl iodide; inasmuch as it melted at 269° C. while the 3-methyl iodmethylate melted at 270° C. A mixture of these two melted at 269° C. (uncor.).

Moreover the product from the addition of methyl iodide to the 4-methoxy must be the same as the 3-methyl-4-quinazolone iodmethylate as it melted at 270° (uncor.). A mixture of these two melted at 270° C. (uncor.).

A mixture of all three melted at 270° C. (uncor.).

They also appeared the same when examined under a microscope.

3-Methyl-4-quinazolone Iodethylate,  $C_6H_4\begin{cases} N(C_2H_5)(I) = CH \\ CO - N.CH_3 \end{cases}$.—

Two grams of the 3-methyl-4-quinazolone were heated with the slight excess over the calculated amount of ethyl iodide at 110° C. for two hours. The tube, on opening, gave no evidence of pressure and it contained a mass of white crystals. They were crystallized from methyl alcohol, being deposited in clusters of small, white needles. This quinazolone is soluble in warm water. A yield of about 40 per cent. of the theory was obtained. It is much more soluble than its isomer the 3-ethyl-4-quinazolone iodmethylate. It melts with evolution of gas at 228° C. (uncor.).

0.2025 gram of substance gave 16.6 cc. of nitrogen at 760 mm. and 25° C.

0.3011 gram of substance gave 0.2235 gram of silver iodide.

	Calculated for $C_{11}H_{13}N_2OI$. Per cent.	Found. Per cent.
Nitrogen	8.86	9.14
Iodine	40.17	40.13

Action of Ethyl Iodide on 4-Methoxyquinazoline.

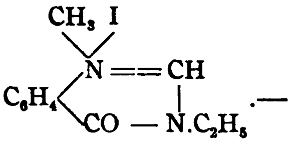
After heating 2 grams of 4-methoxyquinazoline with the calculated amount of ethyl iodide at 100° for several hours, a crystalline product insoluble in cold water was obtained. It crystallized in fine, short needles from methyl alcohol. When dry they form a compact mass resembling glass wool in feeling and appearance. This product melted at 249° C. (uncor.). One gram of product was recovered. An analysis for iodine and nitrogen failed to check with any possible theory and owing to scarcity of mother substance, this experiment was not repeated.

0.2004 gram of substance gave 0.1516 gram of silver iodide.

0.2005 gram of substance gave 0.1517 gram of silver iodide.

0.1521 gram of substance gave 12.8 cc. of nitrogen at 748 mm. and 22° C.

Found.	I. Per cent.	II. Per cent.
Iodine	40.90	40.90
Nitrogen	9.42	. . .

3-Ethyl-4-quinazolone Iodmethylate, 

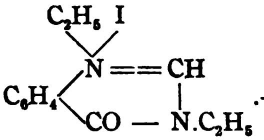
$$C_6H_4\left\langle\begin{array}{l} \overset{CH_3\;\;I}{\overset{\diagdown\diagup}{N}}=\!=CH \\ \qquad\quad\;\;| \\ CO - N.C_2H_5 \end{array}\right. .—$$

The tube containing 3 grams of the 3-ethyl-4-quinazolone with an excess of methyl iodide was heated two hours at 110° C. On opening it contained a solid mass of crystalline structure. It was not very soluble in hot methyl alcohol from which it crystallized in short, thin, white needles with a pearly luster. The yield was 3.1 grams. It was insoluble in cold water, hot acetone, benzol, chloroform and ether; soluble in hot water and hot ethyl alcohol. It melted with evolution of gas at 258° C. (uncor.).

0.3031 gram of substance gave 0.2248 gram of silver iodide.

0.2011 gram of substance gave 16.4 cc. of nitrogen at 748 mm. and 21° C.

	Calculated for $C_{11}H_{13}N_2OI$. Per cent.	Found. Per cent.
Nitrogen	8.86	9.13
Iodine	40.17	40.10

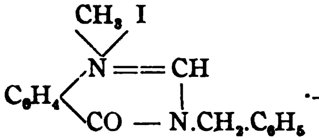
3-Ethyl-4-quinazolone Iodethylate, 

$$C_6H_4\left\langle\begin{array}{l} \overset{C_2H_5\;\;I}{\overset{\diagdown\diagup}{N}}=\!=CH \\ \qquad\quad\;\;| \\ CO - N.C_2H_5 \end{array}\right. .—$$

3-Ethyl-4-quinazolone with the required amount of ethyl iodide heated for two hours at 110° C. gave a solid crystalline mass, colored yellow. This was found to be very soluble in cold methyl alcohol and acetone. It was crystallized, however, from a mixture of methyl alcohol and ether, being deposited in very short, fine, white, needles. In order to do this, the product was dissolved in methyl alcohol, cooled, and enough ether added to form a thick paste. This paste was then carefully heated until all went in solution and allowed to crystallize in an ice pack. It is difficult, however, to obtain a perfectly white compound by this method as it usually possesses a yellow caste. The melting point was found to be 181° C. (cor.). This iodethylate is soluble in cold water, acetone, chloroform, and hot benzol. It is partly soluble in cold ethyl alcohol. 4.5 grams were obtained from 2.75 grams of the starting product which corresponds to 86 per cent. of the theory.

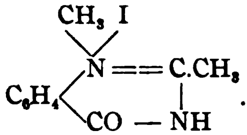
0.3004 gram of substance gave 0.214 gram of silver iodide.

	Calculated for $C_{12}H_{15}N_2OI$. Per cent.	Found. Per cent.
Iodine	38.46	38.51

3-Benzyl-4-quinazolone Iodmethylate, .—A partly amorphous and partly crystalline discolored mass resulted from heating 3 grams of the 3-benzyl-4-quinazolone with methyl iodide for 1 hour at 110° C. This was dissolved in hot ethyl alcohol. On cooling it formed a small ball resembling a fungus growth on one side of the beaker which gradually grew in size until the solution became a semi-solid mass. The yield was 3.3 grams. It was soluble in cold chloroform and hot water; difficultly soluble in hot acetone; insoluble in ether and hot benzol. It melted at 188° C. (cor.).

0.3013 gram of substance gave 0.1866 gram of silver iodide.

	Calculated for $C_{16}H_{15}N_2OI$. Per cent.	Found. Per cent.
Iodine	33.58	33.48

2-Methyl-4-quinazolone Iodmethylate, .—Three grams of the 2-methyl-4-quinazolone were heated for seven hours with a slight excess of methyl iodide at 100° C. On opening the tube no pressure was observed but a hard discolored mass was obtained. This was easily removed without the aid of a solvent. It was found to be very soluble in cold ethyl alcohol, methyl alcohol, and water; insoluble in ether, chloroform, benzol, amyl alcohol, and acetone. Mixtures of methyl alcohol and acetone were tried in various proportions to induce crystallization without any decided success. In one case some very fine, almost microscopic crystals of a yellow color were obtained, but in very small amount. Therefore the substance was extracted several times with amyl alcohol and then acetone, to remove the excess of methyl iodide. This treatment left an amorphous product of yellowish color melting at 220° C. (uncor.). The yield was good by this treatment.

On repeating this experiment to see if a white crystalline product could not be obtained, the heating was carried on 150° C. A hard mass with a crystalline structure was obtained possessed of a deep red color. This was also very soluble in cold methyl alcohol, but if just enough ether was added, so as not to produce an amorphous precipitate and the mixture placed in a freezing mixture at about —10° C., well defined crystals were formed of a white color, melting point 220° C. (uncor.). The yield, however, was rather poor. These crystals remained white for four to five days in the air but gradually changed to a grayish color. This white compound, on analysis, showed that it was the addition product looked for.

0.2006 gram of substance gave 16.6 cc. of nitrogen at 757 mm. and 19° C.

0.3019 gram of substance gave 0.2348 gram of silver iodide.

	Calculated for $C_{10}H_{11}N_2OI$. Per cent.	Found. Per cent.
Nitrogen	9.27	9.47
Iodine	42.03	42.05

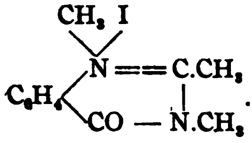
The yellowish product gave the following analysis:

0.1515 gram of substance gave 12.7 cc. of nitrogen at 745 mm. and 24° C.

0.3016 gram of substance gave 0.2353 gram of silver iodide.

	Found. Per cent.
Nitrogen	9.20
Iodine	42.18

2,3-Dimethyl-4-quinazolone Iodmethylate,



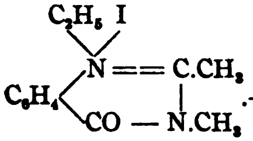
.—To 3 grams of the anhydrous quinazolone was added the calculated amount of methyl iodide and heated in a sealed tube for several hours. No pressure was observed on opening the bomb but the product possessed a slight red color. It was crystallized from methyl alcohol and separated in short, fine, white needles. After three crystallizations, it melted at 242° C. (uncor.) (gas). It is somewhat soluble in cold water, soluble in hot water and hot benzol; insoluble in hot acetone and ether. The yield was 90 per cent. of the theory.

0.1015 gram of substance gave 8.1 cc. of nitrogen at 762 mm. and 23° C.

0.3034 gram of substance gave 0.2269 gram of silver iodide

	Calculated for $C_{11}H_{13}N_2OI$. Per cent.	Found. Per cent.
Nitrogen	8.86	9.01
Iodine	40.18	40.40

2,3-Dimethyl-4-quinazolone Iodethylate,



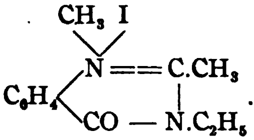
.—In an analogous manner to the above, using ethyl iodide, however, instead of methyl iodide, we obtained a mass of fine crystals colored red. It was thought that if the alkyl halide added to position 3, then addition of ethyl iodide to the 2,3-dimethyl-4-quinazolone would yield the same product as the 2-methyl-3-ethyl-4-quinazolone with methyl iodide. Two distinct products, however, were obtained. On crystallizing from methyl alcohol, it separated in long needles thicker than those obtained from iodmethylates. It was of a pure white color and melted at 237° C. (uncor.) (gas).

0.1517 gram of substance gave 12 cc. of nitrogen at 754 mm. and 23° C.

0.3015 gram of substance gave 0.2147 gram of silver iodide.

	Calculated for $C_{12}H_{15}N_2OI$. Per cent.	Found. Per cent.
Nitrogen	8.48	8.84
Iodine	38.46	38.49

2-Methyl-3-ethyl-4-quinazolone Iodmethylate,



$$C_6H_4\left\langle\begin{array}{l}\overset{CH_3\ \ I}{\overset{\vee}{N}} = C.CH_3 \\ \qquad\qquad | \\ CO - N.C_2H_5\end{array}\right.$$

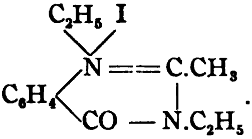
.—When the calculated amount of methyl iodide was added to 2 grams of the 2-methyl-3-ethyl-4-quinazolone, a semi-liquid mass was formed in the tube. After heating at 110° C. for four hours, a crystalline mass of a yellow color appeared. Crystallized from methyl alcohol in which it was more soluble than the 2,3-dimethyl-4-quinazolone iodmethylate, it formed in rosettes of small needles. Owing to its solubility in methyl alcohol, the yield was not so good as the iodmethylates from other quinazolones. It melts with evolution of gas at 217° C. (uncor.).

0.2000 gram of substance gave 15.4 cc. of nitrogen at 760 mm. and 24° C.

0.5025 gram of substance gave 0.3554 gram of silver iodide.

	Calculated for $C_{12}H_{15}N_2OI$. Per cent.	Found. Per cent.
Nitrogen	8.48	8.63
Iodine	38.46	38.24

2-Methyl-3-ethyl-4-quinazolone Iodethylate,



$$C_6H_4\left\langle\begin{array}{l}\overset{C_2H_5\ \ I}{\overset{\vee}{N}} = C.CH_3 \\ \qquad\qquad | \\ CO - N.C_2H_5\end{array}\right.$$

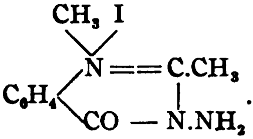
.—On pouring the ethyl iodide on the

2-methyl-3-ethyl-4-quinazolone, it was noticed that it partly dissolved. After heating at 110° C. for 2 hours, a deep red liquid resulted containing a few crystals. The liquid contents of the tube were evaporated and a thick viscous mass remained, which dissolved very readily in both methyl alcohol and acetone, but would not crystallize from either. By adding ether to the methyl alcohol solution, an amorphous precipitate was obtained. This treatment was repeated until a powder of a slight yellow color was obtained. It melted sharply at 177° C. (cor.). The yield was very poor. It was very soluble in cold water.

0.2028 gram of substance gave 0.1392 gram of silver iodide.

	Calculated for $C_{13}H_{17}N_2OI$. Per cent.	Found. Per cent.
Iodine	36.90	37.11

2-Methyl-3-amino-4-quinazolone Iodmethylate,



$$C_6H_4\left\langle\begin{array}{l}\overset{CH_3\ \ I}{\overset{\diagdown\diagup}{N}} = C.CH_3 \\ \qquad\quad | \\ CO - N.NH_2\end{array}\right.$$

.—Before attempting to add methyl iodide to this quinazolone an attempt was made to methylate the amino group using, in two trials, methyl iodide and methyl sulphate, respectively, with caustic potash. After boiling the 2-methyl-3-amino-4-quinazolone for six hours under a reflux in a methyl alcohol solution with caustic and methyl iodide, the litmus still remained blue. On evaporation of the solvent, the original quinazolone was obtained unchanged. When methyl sulphate was used a violent reaction set in, but it was found that no methylation of the amino group had taken place, although an intermediate salt formation took place from which the free amino quinazolone could be obtained by adding a caustic solution.

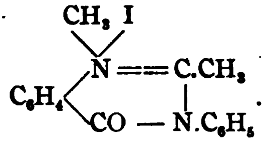
On the first attempt to add methyl iodide the tube was heated for two hours at 110° C. A blackened mass was obtained which dissolved in methyl alcohol but would not crystallize. An attempt to boneblack the solution resulted disastrously, as nothing could be obtained from the filtrate.

On a second trial, the heating was continued only for one hour. A mass of small crystals colored red was found, while considerable pressure had been generated. These crystals were soluble in hot methyl alcohol from which they separated as minute, pink crystals. On evaporation of the mother liquor, rosettes of large crystals were formed. The yield was 2 grams from 3 grams of mother substance. These crystals were soluble in hot water but insoluble in hot chloroform, ether, acetone, and benzol. Melted with evolution of gas at 201° C. (cor.).

0.3008 gram of substance gave 0.2230 gram of silver iodide.

	Calculated for $C_{10}H_{12}N_2OI$. Per cent.	Found. Per cent.
Iodine	40.04	39.93

2-Methyl-3-phenyl-4-quinazolone Iodmethylate,



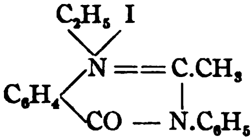
.—Two grams of the 2-methyl-3-phenyl-4-quinazolone treated with methyl iodide at 110° C. formed a hard cake in the tube. This compound was rather difficultly soluble in hot methyl alcohol but crystallized in almost quantitative amount as short needles, sometimes forming in clusters and rosettes. The product has a slight yellow tinge and melts with evolution of gas at 238.5° C. (uncor.). Yield was 90 per cent. of the theory.

0.2013 gram of substance gave 13.4 cc. of nitrogen at 760 mm. and 22° C.

0.4007 gram of substance gave 0.2483 gram of silver iodide.

	Calculated for $C_{16}H_{15}N_2OI$. Per cent.	Found. Per cent.
Nitrogen	7.40	7.54
Iodine	33.58	33.50

2-Methyl-3-phenyl-4-quinazolone Iodethylate,

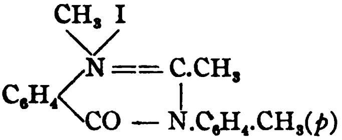


.—On opening the tube after heating the 2-methyl-3-phenyl-4-quinazolone with ethyl iodide for two hours at 110° C., a mass of fine crystals was observed in the tube. They were so very soluble in methyl alcohol that this could not be used for crystallization. However, acetone was found to be suitable for this purpose. Short, white needles were obtained melting with evolution of gas at 236.5° C. (uncor.). The yield was not very good.

0.2032 gram of substance gave 0.1221 gram of silver iodide.

	Calculated for $C_{17}H_{17}N_2OI$. Per cent.	Found. Per cent.
Iodine	32.38	32.49

2-Methyl-3-p-tolyl-4-quinazolone Iodmethylate,

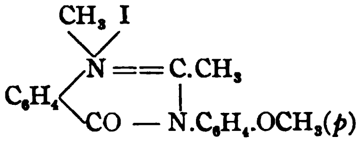


.—When 3 grams of 2-methyl-3-*p*-tolyl-4-quinazolone were heated with methyl iodide at 110° C. for three hours an amorphous slightly colored mass resulted. This dissolved in hot methyl alcohol with difficulty and on cooling long, flat, oblong plates with a satiny luster fell possessing a brilliant salmon color. On recrystallization however, it was seen that the color was mostly due to a small amount of reddish powder which was deposited with the crystals. It was found possible to remove this powder by dissolving the crystals in hot ethyl alcohol in which the red substance did not dissolve. After filtering hot and cooling, the crystals were of a cream color but still possessed the satiny luster. The yield was 3.6 grams which is approximately 80 per cent. of the theory. The crystals were soluble in warm water. Melting point is 234.5° (uncor.) with evolution of gas.

0.3006 gram of substance gave 0.1789 gram of silver iodide.

	Calculated for $C_{17}H_{17}N_2OI$. Per cent.	Found. Per cent.
Iodine	32.38	32.17

2-Methyl-3-p-anisyl-4-quinazolone Iodmethylate,

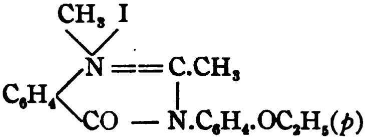


.—2.5 grams of the 2-methyl-3-*p*-anisyl-4-quinazolone were heated for three hours at 116° C. with methyl iodide. There resulted an amorphous discolored mass which crystallized from methyl alcohol in plates of a nacreous luster and possessing a cream color. It was soluble in hot water and hot ethyl alcohol, insoluble in hot acetone, chloroform, ether and benzol. Yield, 3 grams. It melted at 231.5° C. (uncor.) with evolution of gas.

0.3000 gram of substance gave 0.1721 gram of silver iodide.

	Calculated for $C_{17}H_{17}N_2O_2I$. Per cent.	Found. Per cent.
Iodine	31.11	31.01

2-Methyl-3-p-phenetyl-4-quinazolone Iodmethylate,

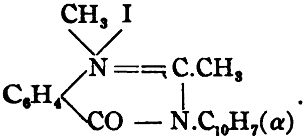


.—2-Methyl-3-*p*-phenetyl-4-quinazolone was heated three hours at 110° C. with excess of methyl iodide. The resulting amorphous hard cake was dissolved in hot methyl alcohol and stood aside for crystallization. Very short needles of a cream color appeared which were soluble in hot ethyl alcohol and hot water but insoluble in hot acetone, benzol, chloroform and ether. The yield was 3.3 grams, melting point 221° C. (uncor.) with evolution of gas.

0.3004 gram of substance gave 0.1670 gram of silver iodide.

	Calculated for $C_{15}H_{19}N_2O_2I$. Per cent.	Found. Per cent.
Iodine	30.07	30.05

2-Methyl-3-α-naphthyl-4-quinazolone Iodmethylate,

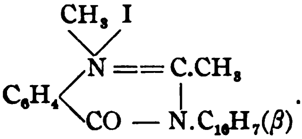


.—Three grams of the 2-methyl-3-α-naphthyl-4-quinazolone heated for three hours at 110° C. yielded an amorphous hard cake in the tube which was rather difficultly soluble in hot methyl alcohol. On cooling there separated minute, cream colored needles, which, when dry, were light and fluffy. Yield, 2 grams. It melted (gas) at 235° C. (uncor.). It was soluble in hot water and ethyl alcohol; insoluble in hot chloroform, acetone, benzol, and ether.

0.3010 gram of substance gave 0.1656 gram of silver iodide.

	Calculated for $C_{20}H_{17}N_2OI$. Per cent.	Found. Per cent.
Iodine	29.65	29.73

2-Methyl-3-β-naphthyl-4-quinazolone Iodmethylate,

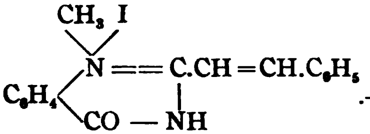


.—A hard, horny mass was obtained from heating 3 grams of 2-methyl-3-β-naphthyl-4-quinazolone for three hours at 120° C. It was ground in a mortar and the resulting powder dissolved in boiling methyl alcohol with difficulty. From this solvent it crystallizes in microscopic needles of a light brown color, soluble in a mixture of hot ethyl alcohol and water. The yield was quantitative. Melting point 238° C. (uncor.) (gas).

0.3005 gram of substance gave 0.1650 gram of silver iodide.

	Calculated for $C_{20}H_{17}N_2OI$. Per cent.	Found. Per cent.
Iodine	29.65	29.80

2-Styryl-4-quinazolone Iodmethylate,

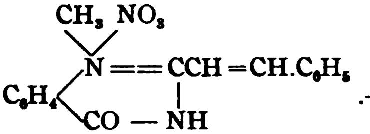


.—It was found that two hours heating of the 2-styryl-4-quinazolone at 110° C. with methyl iodide was sufficient to cause addition. The red and yellow, amorphous solid cake was found to be soluble in hot methyl alcohol from which it crystallizes in short, feathery, orange-yellow needles. In the dry condition they form a compact light mass. The yield was 2.5 grams. It is difficultly soluble in hot water so that for analysis for iodine content a mixture of ethyl alcohol and water was used. It is insoluble in hot ether, chloroform, benzol, and acetone. It begins to fuse at 230° C. and melts to a liquid at 235° C. (uncor.), but unlike the other iodmethylates does not evolve gas.

0.3006 gram of substance gave 0.1803 gram of silver iodide.

	Calculated for $C_{17}H_{15}N_2OI$. Per cent.	Found. Per cent.
Iodine	32.54	32.43

2-Styryl-4-quinazolone-1-methyl Nitrate,



.—In the filtrate from the iodine determination of the above iodmethylate there separated on cooling fine, long, yellow needles. These were filtered by suction and on drying, gave a pure yellow, crystalline product. It melted at 177° C. (cor.) with evolution of gas. Yield was quantitative.

0.1003 gram of substance gave 11.6 cc. of nitrogen at 756 mm. and 23° C.

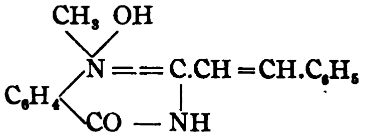
	Calculated for $C_{17}H_{15}N_3O_4$. Per cent.	Found. Per cent.
Nitrogen	12.92	12.96

Attempt to Make the 2-Styryl-4-quinazolonium Hydroxide.

Since all attempts to prepare the quinazolonium hydroxide on the simpler iodmethylates such as, 2,3-dimethyl-4-quinazolone-iodmethylate had failed owing, evidently, to their extreme solubility in water and loss on evaporation, the observance of the formation of the above nitrate led us to attempt the preparation of the hydroxide of the 2-styryl-4-quinazolone.

To this end, 1 gram of the 2-styryl-4-quinazolone iodmethylate was dissolved in about 80 cc. of hot ethyl alcohol and then water was added until a precipitate was about to form, the solution being kept at the boiling point. The calculated amount of freshly precipitated silver oxide was added and in a few minutes had all been converted to the silver iodide. This was filtered hot through a Gooch crucible with suction. On cooling slightly, light yellow crystals immediately separated forming a compact mass. The yield was quantitative. In dry condition it is very light and fluffy and on this account is extremely difficult to handle. It was very soluble in cold chloroform, acetone, ether, benzol, acetic acid. It melted very sharply, but quietly, at 169° C. (cor.). Analysis however, failed to show the presence of the hydroxyl group, the figures obtained pointing towards a formula which had lost a molecule of water.

The calculated values for



$$C_6H_4\left\langle\begin{array}{l}\overset{CH_3\ OH}{\diagdown\diagup}\\ N = = C.CH=CH.C_6H_5 \\ \qquad\quad | \\ CO - NH\end{array}\right.$$

are

N	10.00
C	72.85
H	5.71

The figures obtained by analyses were:

0.1208 gram of substance gave 11.3 cc. of nitrogen at 765 mm. and 19° C.

0.1004 gram of substance gave 9.6 cc. of nitrogen at 765 mm. and 24° C.

0.1486 gram of substance gave 0.4171 gram of CO_2 and 0.0715 gram of H_2O.

0.1614 gram of substance gave 0.4529 gram of CO_2 and 0.0693 gram of H_2O.

0.1538 gram of substance gave 0.4313 gram of CO and 0.070 gram of water.

These values obtained point to the loss of a molecule of water which would give the resulting compound a formula of $C_{17}H_{14}N_2O$. The values for carbon are low however.

	Calculated for $C_{17}H_{14}N_2O$. Per cent.	Found. Per cent. I.	II.	III.
Nitrogen	10.68	10.82	10.80	....
Carbon	77.86	76.55	76.52	76.47
Hydrogen	5.34	5.34	4.77	5.00

The fact that this substance could not be the hydroxide was substantiated by the following experiments:

One gram of the 2-styryl-4-quinazolone iodmethylate was suspended in cold absolute ethyl alcohol and the calculated amount of metallic sodium, dissolved in another portion of absolute alcohol, added. All the iodmethylate immediately went into solution, but after standing a minute, a crystalline, feathery compound appeared. This was filtered, dried and found to melt at 169° C. (cor.). A mixture of this compound with that obtained above also melted at 169° C. (cor.).

Moreover, as it was found possible, as described above, to replace the iodine by a NO_3 group, it was thought possible to replace the iodine by a SO_4 or acetate radicle. This, however, was not the case, as in both instances a light yellow, feathery compound was obtained which melted sharply at 169° C. (cor.), the same as when with silver oxide was used.

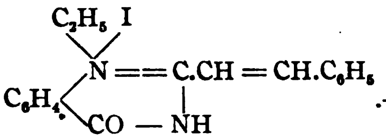
One gram of the 2-styryl iodmethylate was dissolved in hot glacial acetic acid and silver acetate added. The filtrate from the silver iodide was evaporated to a small volume but no crystallization took place. Dilution with cold water however, caused a product to separate which melted at 169° C. (cor.).

A small portion of this was dissolved in a warm acetic anhydride from which nothing separated on cooling. Dilution with ether caused no change. After standing a few days, during which time the ether and most of the acetic anhydride had evaporated spontaneously, clusters of fine, yellow, feathery crystals of the starting product were obtained. Melting point 169° C. (cor.).

Silver sulphate in water and alcohol solution gave the same result.

A molecular weight determination showed that no dimolecular condensation had taken place.

2-Styryl-4-quinazolone Iodethylate,



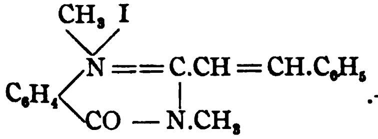
$$\begin{array}{l} \qquad C_2H_5\ \ I \\ \qquad\ \ \diagdown\diagup \\ \qquad\ \ N == C.CH = CH.C_6H_5 \\ C_6H_4\langle \qquad\quad | \\ \qquad\ \ CO - NH \end{array}$$

.—When the heating of the 2-styryl-4-quinazolone was continued for three hours at 110° C. with ethyl iodide, no addition took place. Therefore it was continued for ten hours at 140° C. and an orange colored product resulted in the tube. It is much more soluble in methyl alcohol than the corresponding iodmethylate which it resembles very much. It crystallizes from a small amount of methyl alcohol in small, feathery, orange needles. The yield was 1.5 grams from 3 grams of mother substance. It is insoluble in cold water, rather difficultly soluble in hot water, partly soluble in hot acetone and chloroform; insoluble in hot benzol and ether. Melts at 217°–18° C. (uncor.); no gas.

0.3020 gram of substance gave 0.1757 gram of silver iodide.

	Calculated for $C_{18}H_{17}N_2OI$. Per cent.	Found. Per cent.
Iodine	31.41	31.45

2-Styryl-3-methyl-4-quinazolone Iodmethylate,



$$\begin{array}{l} \qquad CH_3\ \ I \\ \qquad\ \ \diagdown\diagup \\ \qquad\ \ N == C.CH = CH.C_6H_5 \\ C_6H_4\langle \qquad\quad | \\ \qquad\ \ CO - N.CH_3 \end{array}$$

.—Two grams of the 2-styryl-3-

methyl-4-quinazolone were heated with the calculated amount of methyl iodide in a sealed tube for four hours at 110° C. No pressure was observed on opening the tube while the contents were a solid, amorphous mass. This was dissolved in methyl alcohol and on cooling bright yellow leaflets separated. It is soluble in a large amount of hot water. The yield was 80 per cent. of the theory. Melts with evolution of gas at 210° C. (uncor.).

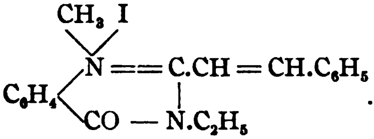
0.2001 gram of substance gave 12.4 cc. of nitrogen at 760 mm. and 17° C.

0.3016 gram of substance gave 0.1757 gram of silver iodide.

	Calculated for $C_{18}H_{17}N_2OI$. Per cent.	Found. Per cent.
Nitrogen	6.93	7.19
Iodine	31.41	31.49

An attempt to obtain the iodethylate failed, for after heating the 2-styryl-3-methyl-4-quinazolone for five hours at 140°–150° with an excess of ethyl iodide, only the original substance was obtained.

2-Styryl-3-ethyl-4-quinazolone Iodmethylate,

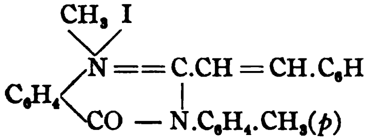


.—Heating 2 grams of the 2-styryl-3-ethyl-4-quinazolone for two hours at 115° C. gave a solid mass in the tube. It crystallizes from methyl alcohol in golden yellow plates but is much more soluble than the 2-styryl-3-methyl-4-quinazolone iodmethylate. It is rather insoluble in cold water and not readily soluble in hot. The yield was about 30 per cent. of the theory. Melting point 207.5° C. (uncor.) (gas).

0.2020 gram of substance gave 0.1138 gram of silver iodide.

	Calculated for $C_{19}H_{19}N_2OI$. Per cent.	Found. Per cent.
Iodine	30.36	30.46

2-Styryl-3-p-tolyl-4-quinazolone Iodmethylate,



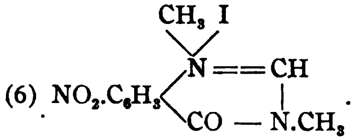
.—When the 2-styryl-3-*p*-tolyl-4-quinazolone was heated with methyl iodide for three hours at 110° C. it was unattacked. However, on repeating at 140° C. for ten hours a partly crystalline, discolored mass resulted. It is more soluble in methyl alcohol, than the 2-methyl-3-*p*-tolyl-4-quinazolone iodmethylate and forms in clusters of canary-yellow needles of large size. It is soluble in hot ethyl alcohol, difficultly in hot water; insoluble in hot chloroform, acetone, ether and benzol. Melts at 219.5° C. (uncor.) with evolution of gas.

0.3006 gram of substance gave 0.1473 gram of silver iodide.

	Calculated for $C_{24}H_{21}N_2OI$. Per cent.	Found. Per cent.
Iodine	26.50	26.49

Other styryl derivatives tried with methyl iodide at 140° for ten hours but which failed to add were: 2-styryl-3-phenyl-4-quinazolone, 2-styryl-3-*p*-anisyl-4-quinazolone, 2-styryl-3-*p*-phenetyl-4-quinazolone, and 2-styryl-3-α-naphthyl-4-quinazolone.

6-Nitro-3-methyl-4-quinazolone Iodmethylate,



.—Six grams of the 6-nitro-3-methyl-4-quinazolone were heated six hours at 130° C. with methyl iodide. There was no pressure and the contents of the tube were a dark brown mass moistened with methyl iodide. On crystallizing from methyl alcohol, long needles of an orange-red color separated in clusters, radiating from a common center. This product after recrystallization from either methyl or ethyl alcohol gave the following analyses: (The results are on two separate preparations of this compound.) The melting point was 228.5° C. (uncor.) and yield, 5 grams.

0.1025 gram of substance gave 14.6 cc. of nitrogen at 760 mm. and 25° C.

0.1022 gram of substance gave 14.4 cc. of nitrogen at 754 mm. and 21° C.

0.2018 gram of substance gave 0.0872 gram of silver iodide.

0.2026 gram of substance gave 0.0880 gram of silver iodide.

	Found. Per cent.	
	I.	II.
Iodine	15.80	15.90
Nitrogen	23.36	23.43

While these analyses checked, the figures obtained were far from the theoretical values for the 6-nitro-2-methyl-4-quinazolone iodmethylate which are:

	N.	I.
Calculated for $C_{10}H_{10}N_3O_3I$	12.10	36.58

They approximate fairly closely values which would be obtained if one molecule of 6-nitro-3-methyl-4-quinazolone and one molecule of the 6-nitro-3-methyl-4-quinazolone iodmethylate were present together in some combination. The theory for such a mixture would be N = 15.21 per cent. and I = 23.00 per cent.

Moreover, that some kind of a combination actually does exist can be shown by the microscope as the crystals appeared entirely homogeneous. The sharpness and constancy of the melting point also argued for a definite compound.

Nevertheless when 1 gram of this orange-red compound was boiled with about 80 cc. of water, all dissolved. On cooling a cream colored substance separated which proved by its melting point and absence of halogen to be the mother substance, *i. e.*, the 6-nitro-3-methyl-4-quinazolone. Of this, 0.270 gram were recovered. On evaporating the mother liquor to about 30 cc., 0.20 gram of the orange-red product separated. The sum of these two recovered show that still something must be left in the mother liquor. Consequently on evaporating still further to about 10 cc. long needles of a yellow compound separated which melted sharply also at 228.5° C. On analysis, this proved to be the iodmethylate sought for.

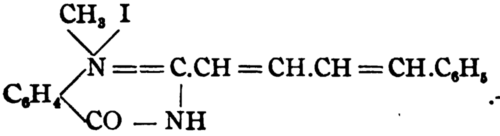
0.3000 gram of substance gave 0.2008 gram of silver iodide.

	Calculated for $C_{10}H_{10}N_3O_3I$. Per cent.	Found. Per cent.
Iodine	36.58	36.19

However, the fact that this yellow iodmethylate melts exactly the same as the orange-red compound first obtained has not been accounted for.

It was found that the 6-nitro-2-methyl-4-quinazolone, the 6-nitro-2,3-dimethyl-4-quinazolone, and the 6-nitro-2-methyl-3-ethyl-4-quinazolone would not add methyl iodide, although different temperature and times of heating were tried.

1-(4-Quinazolonyl)-4-phenyl-1,3-butydiene Iodmethylate,



$$C_6H_4\begin{cases}\overset{CH_3\ \ I}{\overset{\diagdown\diagup}{N}} = C.CH = CH.CH = CH.C_6H_5 \\ \qquad\quad | \\ CO - NH\end{cases}$$

.—Two grams of the 1-(4-quinazolonyl)-4-phenyl-1,3-butydiene were heated at 120° C. for three hours in a bomb with methyl iodide. A dark red, amorphous mass was obtained which was soluble in hot methyl alcohol. It separated from this solvent in minute, crystalline needles of a brick-red color. The yield was 1 gram. It was insoluble in hot water but soluble in a mixture of water and ethyl alcohol. It melted with slight evolution of gas at 232.5° C. (uncor.).

0.3008 gram of substance gave 0.1693 gram of silver iodide.

	Calculated for $C_{19}H_{17}N_2OI$. Per cent.	Found. Per cent.
Iodine	30.51	30.43

Product from the Above.

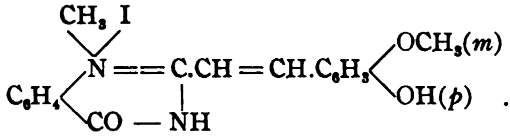
In the filtrate from the iodine determination of the above there separated, on cooling, thin, orange-yellow, feathery needles melting quietly at 167° C. (cor.) to a clear liquid. It was thought that this might be the methyl nitrate addition as obtained in the same manner from the 2-styryl-4-quinazolone iodmethylate. The melting point, however, showed that it could not be the nitrate as it did not give off any gas as the styryl methyl nitrate product did, but melted quietly. A nitrogen determination also showed that it was not the methyl nitrate addition. It was thought, therefore, that another compound analogous to that obtained from the 2-styryl-4-quinazolone iodmethylate by means of silver oxide had resulted. A nitrogen determination pointed toward this fact.

The compound with a loss of a molecule of water would have the empirical formula, $C_{19}H_{16}N_2O$.

0.0833 gram of substance gave 7.4 cc. of gas at 757 mm. and 24° C.

	Calculated for $C_{19}H_{16}N_2O$. Per cent.	Found. Per cent.
Nitrogen	9.72	9.91

2-m-Methoxy-p-oxy-styryl-4-quinazolone Iodmethylate,



$$C_6H_4\left<\begin{array}{l} \overset{CH_3\ I}{\diagdown\!\diagup} \\ N == C.CH = CH.C_6H_3\left<\begin{array}{l}OCH_3(m)\\ OH(p)\end{array}\right. \\ \quad\quad\ \ | \\ CO - NH \end{array}\right.$$

.—Two grams of the 2-*m*-methoxy-*p*-oxy-styryl-4-quinazolone were heated in a bomb for three hours at 120° C. with methyl iodide. The tube contained a deep reddish mass easily soluble in hot methyl alcohol, from which it crystallized in bright red, microscopic crystals. The yield was 2.5 grams. The product melted quietly at 223–25° C. (uncor.). It is not very soluble in hot water but dissolves in a mixture of hot ethyl alcohol and water.

0.3030 gram of substance gave 0.1617 gram of silver iodide.

	Calculated for $C_{18}H_{17}N_2O_3I$. Per cent.	Found. Per cent.
Iodine	29.11	28.82

It was hoped that the methyl nitrate addition product would separate from the filtrate, but nothing was obtained, until it had been evaporated to a small volume, when a microscopic, crystalline, red substance was obtained in small quantity. It possessed a red color, but on drying, at 110° C. it became brown and melted with evolution of gas at 175° C. (uncor.). This has not been analyzed but is probably the methyl nitrate addition as was obtained from the 2-styryl-4-quinazolone.

III.

NITRATION OF SOME QUINAZOLONES.

INTRODUCTION.

As an introduction to the nitroquinazolones already prepared, we are unable to improve on the introduction given by Klaber[19] in his dissertation on the "7-Nitroquinazolones." We therefore quote from him in part.

"The quinazolones or benzomiazines present the possibility of four isomeric *bz*-mononitro derivatives, all of which have been synthesized in the 2-methyl-4-quinazolone group.

Griess,[20] in 1869, obtained the ethyl ether of an acid, $C_8H_6N_2O_2$, by passing cyanogen gas into a saturated alcoholic solution of anthranilic acid; he obtained the acid itself and nitrated it. It was proved later that his acid was benzoylene urea, but the position of the nitro group in the derivative which he obtained has never been determined. In 1890, DeHoff[21] nitrated the anhydroacetylorthoaminobenzamide of Weddige[2] (2-methyl-4-quinazolone) and obtained thereby a mononitro derivative. By the action of methyl iodide upon its potassium salt and by direct nitration of the 2,3-dimethyl-4-quinazolone the corresponding nitro-2,3-dimethyl-4-quinazolone was prepared. The positin of the nitro group in these compounds remained unproved until, in 1891, Thieme[22] obtained the same products by the action of ammonia and methylamine on 5-nitroacetanthranilic ester. This showed DeHoff's compounds to be the 6-nitro-quinazolones.

In his work upon 3-nitroanthranilic ester, Zacharias[23] synthesized 8-nitroquinazolones by the action of ammonia and primary amines upon 3-nitroacetanthranilic ester and 3-nitrobenzoylanthranilic ester. In 1896 Kratz[24] obtained a 6-nitro-3-amino-4-quinazolone by the action of glacial formic acid on 5-nitroanthranilic hydrazide.

The contribution from the Havemeyer laboratories of Columbia University include the syntheses of the 5-nitro, 6-nitro, and 7-nitro quinazolones from 6-nitro, 5-nitro and 4-nitro acetanthranils respectively. They were prepared by the reaction of Anschütz, Schmidt, and Greiffenberg[10] between acetylanthranil and primary amines. The work on the 5-nitro derivatives was carried on by Bogert and Chambers[25] and Bogert and Seil,[26] on the 6-nitro compounds by Bogert and Cook[27] and on the 7-nitroquinazolones by Bogert and Steiner[28]'' and Bogert and Klaber.[29]

As to the reduction products from the nitroquinazolones, DeHoff[21] tried to reduce his 6-nitro-2-methyl-4-quinazolone but failed to do so.

Zacharias,[28] by using tin or stannous chloride in a hydrochloric acid solution, reduced the 8-nitro-2-methyl-4-quinazolone. This aminoquinazolone crystallizes from water in colorless needles, melting at 230°–2° but Zacharias was unable to separate the last traces of tin, so he did not get good analytical figures.

On reducing the 5-nitro-2-methyl-4-quinazolone with stannous chloride in a hydrochloric acid solution, Bogert and Chambers[30] prepared 5-amino-2-methyl-4-quinazolone and 5-amino-4-quinazolone; the former melting at 295–310° C. with one molecule of water of crystallization.

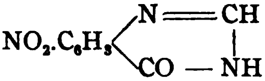
Bogert and Klaber[29] were able to reduce the 7-nitro-2-methyl-4-quinazolone to the corresponding amino derivatives in the same manner as above. It melts at 311° C. (cor.).

As to the 6-amino-2-methyl-4-quinazolone, Bogert and Amend[31] prepared 4-acetamino acetanthranil from 2,4-diacetaminobenzoic acid. By condensing this anthranil with ammonia they obtained the 6-acetamino-2-methyl-4-quinazolone which on treatment with 10 per cent. potassium hydroxide solution yielded the 6-amino-2-methyl-4-quinazolone

On carrying out nitrations on a number of quinazolones, we found in accordance with DeHoff's[21] and Thiemes'[22] work that the entering nitro group goes in position 6 on the benzol nucleus of the quinazolone cycle. Further that when another benzol ring is present as in 2-methyl-3-phenyl-4-quinazolone, that two nitro groups enter, the location of which we have not been able to prove.

From the above nitrated products by reduction we have prepared a number of 6-amino quinazolones which we believe to be new.

Experimental Part.

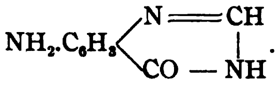
6-Nitro-4-quinazolone, (6)  $NO_2.C_6H_3{<}\begin{array}{l} N = CH \\ \quad\;\; | \\ CO - NH \end{array}$. — When 4-quinazolone was added to fuming nitric acid (1.6 sp. gr.) no nitration took place, the unchanged quinazolone being recovered. Consequently 5 grams of the 4-quinazolone were added cautiously in small portions to 20 cc. of a mixture of equal parts of fuming nitric acid (1.6 sp. gr.) and concentrated sulphuric acid. The quinazolone dissolved with a violent hissing sound while nitrous fumes were simultaneously evolved. This mixture was then evaporated to about one-half the original volume and, after cooling, was poured in a large volume of cold water. On cooling beautiful, large, pearly flakes or plates separated until finally a semi-solid mass was formed. When these crystals were filtered and washed with water they lost their luster and fell to a yellow powder. This product was purified by dissolving in dilute caustic potash giving a dark red color, and reprecipitated by adding glacial acetic acid to the neutral point. Thus purified it possessed a slight cream color. The yield was about 60 per cent. of the theory. It is partially soluble in hot water, ethyl and methyl alcohol; insoluble in ether, chloroform and benzol. It takes on a brown color at 275° and melts with decomposition at 284° C. (uncor.).

0.2017 gram of substance gave 39 cc. of nitrogen at 762 mm. and 25° C.

0.1028 gram of substance gave 19.8 cc. of nitrogen at 764 mm. and 20° C.

	Calculated for $C_8H_5N_3O_3$. Per cent.	Found. Per cent. I	II
Nitrogen	21.99	21.63	22.15

6-Amino-4-quinazolone, (6)



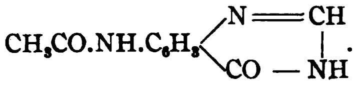
$$NH_2.C_6H_3\left\langle\begin{array}{l}N=CH\\ \quad\quad\ \ |\\ CO-NH\end{array}\right.$$

.—To a saturated hydrochloric acid solution of twice the calculated amount of stannous chloride were added 2 grams of the 6-nitro-4-quinazolone in small portions. Considerable heat was developed. The solution was then heated to drive off the excess of hydrochloric acid and during this operation a white crystalline precipitate appeared. This was probably the tin double salt. On pouring into about 100 cc. of water, it dissolved, and hydrogen sulphide was passed into the warm solution until all the tin had been precipitated. The clear solution was made distinctly alkaline with caustic potash and a green precipitate (probably iron) which appeared was filtered off. By exactly neutralizing with hydrochloric acid, long, white, thin needles separated which were recrystallized from hot water. These melted at 317°–18° C. (cor.). The yield was about 20 per cent. of the theory.

0.1020 gram of substance gave 24.2 cc. of nitrogen at 746 mm. and 25° C.

	Calculated for $C_8H_7N_3O$. Per cent.	Found. Per cent.
Nitrogen	26.08	25.95

6-Acetamino-4-quinazolone (6)



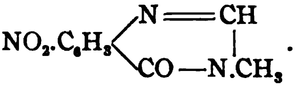
$$CH_3CO.NH.C_6H_3\left\langle\begin{array}{l}N=CH\\ \quad\quad\ \ |\\ CO-NH\end{array}\right..$$

—The 6-amino-4-quinazolone was dissolved with the aid of heat in a small amount of acetic anhydride and the excess boiled off. When cool, this was poured into cold water and the 6-acetamino-4-quinazolone separated in short, white, silky needles. Recrystallized from hot water, it melted at 335° C. (cor.). The yield was 90 per cent. of the theory.

0.1013 gram of substance gave 18.5 cc. of nitrogen at 771 mm. and 26° C.

	Calculated for $C_{10}H_9N_3O_2$. Per cent.	Found. Per cent.
Nitrogen	20.69	20.57

6-Nitro-3-methyl-4-quinazolone, (6)



$$NO_2.C_6H_3\left\langle\begin{array}{l}N = CH\\ \qquad\quad |\\ CO-N.CH_3\end{array}\right.$$

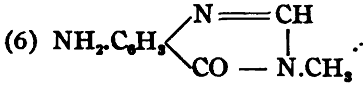
—By methylation, 5 grams of the 6-nitro-4-quinazolone were added to 125 cc. of methyl alcohol containing the calculated amount of potassium hydroxide and then methyl iodide, in required amount, was poured in the flask. On heating, the quinazolone went into solution and after boiling gently for two hours, yellow crystals began to separate. The heating was discontinued and further crystallization took place on cooling. This product was recrystallized from methyl alcohol and then melted at 196° C. (cor.).

By nitration. In order to see if the same compound as the above could be obtained by nitration of the 3-methyl-4 quinazolone, 5 grams of the anhydrous 3-methyl-4-quinazolone were added to 20 cc. of a mixture consisting of one-third concentrated sulphuric acid and two-thirds fuming nitric acid (1.6 sp. gr.). After driving off the excess fumes and concentrating to one-third of the volume, the reaction mixture was poured into cold water. Fine crystals separated in fan-like clusters at first, but the liquid soon became a semi-solid mass. Some of the product was crystallized from hot water and yielded cream-colored needles melting at 196° C. (cor.). A mixture of the compound obtained in this manner mixed with that obtained by methylation also melted at 196° C. (cor.). It is soluble in hot ethyl alcohol, acetone and benzol, insoluble in cold ethyl alcohol and ether. The yield was about 70 per cent. of the theory.

0.1034 gram of substance gave 19.3 cc. of nitrogen at 770 mm. and 29° C.

	Calculated for $C_9H_7N_3O_3$. Per cent.	Found. Per cent.
Nitrogen	20.48	20.64

6-Amino-3-methyl-4-quinazolone,



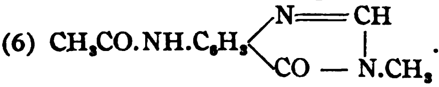
$$\text{(6) NH}_2\text{.C}_6\text{H}_3\left\langle\begin{array}{l} \text{N}=\!=\text{CH} \\ \qquad\quad | \\ \text{CO}-\text{N.CH}_3\end{array}\right.$$

.—The 6-nitro-3-methyl-4-quinazolone was reduced by adding 3 grams to the calculated amount of stannous chloride dissolved in concentrated hydrochloric acid. Although heat was developed, the mixture was warmed awhile longer to complete the reaction. During the heating white crystals were formed but were not isolated. These were dissolved in about three times the volume of warm water and hydrogen sulphide passed in until all the tin had been removed. The solution was then heated to remove the hydrogen sulphide and made alkaline, keeping the solution hot. A precipitate of ferrous hydroxide was filtered off. On cooling, the amino derivative separated in small, white needles. Recrystallization from water yielded a product melting at 209° C. (uncor.). Yield, 20 per cent. of the theory.

0.1020 gram of substance gave 21.9 cc. of nitrogen at 764 mm. and 26° C.

	Calculated for $C_9H_9N_3O$. Per cent.	Found. Per cent.
Nitrogen	24.00	23.96

6-Acetamino-3-methyl-4-quinazolone,



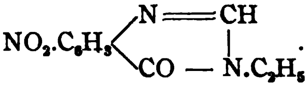
$$\text{(6) CH}_3\text{CO.NH.C}_6\text{H}_3\left\langle\begin{array}{l} \text{N}=\!=\text{CH} \\ \qquad\quad | \\ \text{CO}-\text{N.CH}_3\end{array}\right.$$

.—The above amino derivative was acetylated by heating it with acetic anhydride until dissolved, and pouring the solution into a small amount of cold water. As the product did not separate after standing a short time, the solution was partially neutralized with caustic potash until the white precipitate was obtained. White, silky needles were obtained on crystallization from hot water. It melted at 269° C. (uncor.). The yield was very good.

0.1015 gram of substance gave 17.6 cc. of nitrogen at 757 mm. and 23° C.

	Calculated for $C_{11}H_{11}N_3O_2$. Per cent.	Found. Per cent.
Nitrogen	19.35	19.47

6-Nitro-3-ethyl-4-quinazolone, (6)



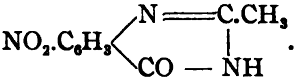
$$NO_2.C_6H_3\left\langle\begin{array}{l} N = CH \\ \quad\quad\ \ | \\ CO - N.C_2H_5 \end{array}\right. .$$

To a mixture of 5 cc. of concentrated sulphuric acid and 15 cc. of fuming nitric acid (1.52 sp. gr.) were added, in portions, 2 grams of the 3-ethyl-4-quinazolone and the mixture evaporated to one-half its original bulk. On pouring into cold water, the product crystallized in fine needles but, washing with water causes it to become amorphous. It crystallizes from hot water in which it is not very soluble, in both short and long, thin needles. When dry, it has a slight yellow color. The yield was 1.2 grams which is 47 per cent. of the theory. It melted at 165° C. (cor.). It is also soluble in hot ethyl alcohol.

0.1005 gram of substance gave 16.9 cc. of nitrogen at 760 mm. and 19° C.

	Calculated for $C_{10}H_9N_3O_3$. Per cent.	Found. Per cent.
Nitrogen	19.18	19.33

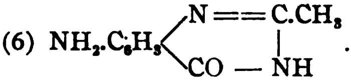
6-Nitro-2-methyl-4-quinazolone, (6)



$$NO_2.C_6H_3\left\langle\begin{array}{l} N = C.CH_3 \\ \quad\quad\ \ | \\ CO - NH \end{array}\right. .$$

—DeHoff's[21] directions for nitration were followed. The product was purified by dissolving in dilute caustic potash and precipitating by the addition of acetic acid. Thus purified it melted with decomposition at 299° C. (uncor.), and takes on a brown color about 266°. DeHoff stated that his product assumed a deep brown color at 280° C., but gives no melting point. Bogert and Cook[27] made the 6-nitro-2-methyl-4-quinazolone from 5-nitro-acetanthranil by condensing it with ammonia and give the melting point as 278°–81° C. (cor.). On repeated trials we always obtained the same melting point as given above. This has also been substantiated by other workers in the laboratory.

6-Amino-2-methyl-4-quinazolone,



$$(6)\ NH_2.C_6H_3\left\langle\begin{array}{l} N == C.CH_3 \\ \qquad\quad | \\ CO - NH \end{array}\right.$$

.—DeHoff[21] states that a trial which he made to reduce his 6-nitro-2-methyl-4-quinazolone failed.

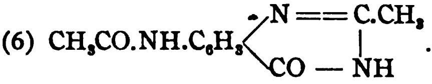
Two grams of this nitroquinazolone were treated with stannous chloride in exactly an analogous manner as the 6-nitro-4-quinazolone. The product crystallized from hot water in long, thin needles but the yield was rather poor.

At about the same time as this reduction product was obtained, Bogert and Amend[31] prepared it by treating the 6-acetamino-2-methyl-4-quinazolone with caustic potash solution. They found their product softened at 314° C. (cor.) and melted at 314°–15° C. (cor.). We found the same figures as given by them. A mixture of their product with ours melted at 314° C. (cor.) thus establishing them as identical.

0.1002 gram of substance gave 21.3 cc. of nitrogen at 758 mm. and 21° C.

	Calculated for $C_9H_9N_3O$. Per cent.	Found. Per cent.
Nitrogen	24.00	24.12

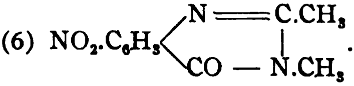
6-Acetamino-2-methyl-4-quinazolone,



$$(6)\ CH_3CO.NH.C_6H_3\left\langle\begin{array}{l} N == C.CH_3 \\ \qquad\quad | \\ CO - NH \end{array}\right.$$

.—By acetylating the 6-amino-2-methyl-4-quinazolone obtained by reduction by means of acetic anhydride, we obtained fine, white needles. The melting point was 351° C. (cor.). This was the same as Bogert and Amend[31] obtained from 5-acetamino anthranil and ammonia. They give 350° C. (cor.). A mixture of their substance with ours melted at 349° C. (cor.).

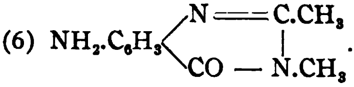
6-Nitro-2,3-dimethyl-4-quinazolone,



$$(6)\ NO_2.C_6H_3\left\langle\begin{array}{l} N == C.CH_3 \\ \qquad\quad | \\ CO - N.CH_3 \end{array}\right.$$

.—This quinazolone had been obtained by DeHoff[21] by methylation of the 6-nitro-2-methyl-4-quinazolone, by Thieme,[22] from 5-nitroorthoacetaminobenzoic acid ethyl ester and methylamine; by Bogert and Cook[27] from 5-nitroacetanthranil and methylamine. They all obtained 165° C. (cor.) as a melting point. By nitration, using a mixture of concentrated sulphuric and fuming nitric acids, we also obtained a light yellow product melting at 164°-165° C. (cor.).

6-Amino-2,3-dimethyl-4-quinazolone,



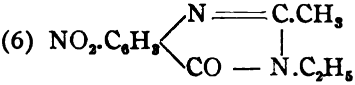
$$(6)\ NH_2.C_6H_3\left\langle\begin{array}{l}N = C.CH_3\\ \qquad\quad |\\ CO - N.CH_3\end{array}\right.$$

.—This reduction was accomplished in the same way as the nitro-3-methyl-4-quinazolone. The amino product crystallizes from an alkaline solution in thin, white, silky needles, melting after recrystallization from hot water at 244° C. (uncor.). Yield, 10 per cent.

0.1004 gram of substance gave 19.3 cc. of nitrogen at 768 mm. and 19° C.

	Calculated for $C_{10}H_{11}N_3O$. Per cent.	Found. Per cent.
Nitrogen	22.22	22.33

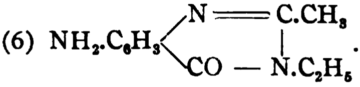
6-Nitro-2-methyl-3-ethyl-4-quinazolone,



$$(6)\ NO_2.C_6H_3\left\langle\begin{array}{l}N = C.CH_3\\ \qquad\quad |\\ CO - N.C_2H_5\end{array}\right.$$

.—As the 2-methyl-3-ethyl-4-quinazolone had been but recently prepared it had not been nitrated. Five grams were added to a mixture of 15 cc. of concentrated sulphuric acid and 20 cc. of fuming nitric acid (1.52 sp. gr.) and the excess of nitric boiled off. After pouring into a large volume of cold water, the nitro compound came down in short, fine needles but fell to an amorphous powder when washed with water. The yield was 80 per cent. of the theory. It has a yellow color and melts at 166° C. (cor.) as given by Bogert and Cook[27] who prepared it from 5-nitroacetanthranil and ethylamine.

6-Amino-2-methyl-3-ethyl-4-quinazolone,



$$(6)\ NH_2.C_6H_3\left\langle\begin{array}{l}N = C.CH_3\\ \qquad\quad |\\ CO - N.C_2H_5\end{array}\right.$$

.—The 6-nitro-2-methyl-3-ethyl-4-quinazolone was reduced in the same manner as the other nitro compounds. It crystallized from hot water in long, thin, white needles melting at 183° C. (uncor.). The yield was 20 per cent. of the theory.

0.1001 gram of substance gave 18.4 cc. of nitrogen at 761 mm. and 24° C.

	Calculated for $C_{11}H_{13}N_3O$. Per cent.	Found. Per cent.
Nitrogen	20.69	20.63

Nitration of the 2-Methyl-3-phenyl-4-quinazolone.

The 2-methyl-3-phenyl-4-quinazolone was nitrated in the same manner as the above using one-third concentrated sulphuric and two-thirds fuming nitric acids. After boiling down, the reaction mixture was poured into cold water and the nitrated product separated in very fine needle-like crystals of a yellow color. This compound was insoluble in hot water, ethyl alcohol, methyl alcohol, ether, benzol, and chloroform; soluble in hot acetone, from which it separates in microscopic needles and hot glacial acetic acid, also coming down in microscopic crystals. The yield was 65 per cent. of the theory. It melted with decomposition at 267° C. (uncor.). Since the 6-nitro-2-methyl-3-phenyl-4-quinazolone prepared by Bogert and Cook[27] melted at 220° C. (cor.) it was suspected that a dinitro derivative had been obtained. A Dumas nitrogen confirmed this idea.

0.1003 gram of substance gave 15.4 cc. of nitrogen at 748 mm. and 21° C.

	Mononitro. Calculated for $C_{15}H_{11}N_3O_3$. Per cent.	Dinitro. Calculated for $C_{15}H_{10}N_4O_5$. Per cent.	Found. Per cent.
Nitrogen	14.94	17.17	17.21

Nitration of 2-Methyl-3-p-nitrophenyl-4-quinazolone.

As it was suspected that in the nitration of the 2-methyl-3-phenyl-4-quinazolone one of the nitro groups had entered position 6 on the benzol nucleus of the quinazolone cycle and the other had entered the *p*-position on the phenyl nucleus attached to position 3, it was thought that by nitration of 2-methyl-3-*p*-nitrophenyl-4-quinazolone one more nitro group would enter in position 6. On nitrating this quinazolone only one more nitro group did enter but the resulting dinitro compound melting at 264° was different than that obtained by nitration of 2-methyl-3-phenyl-4-quinazolone melting at 267° (uncor.). A mixture of the two melted at 225° C. (uncor.). This result suggests then that one of two nitro groups entering on nitration of 2-methyl-3-phenyl-4-quinazolone entered the *m*-position on the phenyl nucleus. Unfortunately we were unable to prepare 2-methyl-3-*m*-nitrophenyl-4-quinazolone so we were not able to prove this point.

This product was precipitated almost as soon as the reaction mixture was added to water. It is insoluble in hot water and ethyl alcohol. It crystallizes from glacial acetic acid in small clusters of small needles of a yellow color. Melts at 264° C. (uncor.) with decomposition.

0.1008 gram of substance gave 15.7 cc. of nitrogen at 747 mm. and 22° C.

Calculated for $C_{15}H_{10}N_4O_5$. Per cent.	Found. Per cent.
17.17	17.34

Nitration of 2-Methyl-3-paratolyl-4-quinazolone.

Inasmuch as in nitration of the 2-methyl-3-paranitrophenyl-4-quinazolone only one nitro group was introduced, it was decided to try nitration of the 2-methyl-3-paratolyl-4-quinazolone in which the para position of the phenyl nucleus in 3 was also occupied.

Consequently 2 grams of this quinazolone were added to a mixture of concentrated sulphuric acid and fuming nitric acid (sp. gr. 1.52) and the excess of nitric acid expelled. On pouring into cold water, the product separated as an amorphous, yellow powder. It was insoluble in hot water and ethyl alcohol but soluble in hot glacial acetic acid from which it separated only on addition of water in an amorphous condition. The yield was 1.2 grams. It begins to shrivel at 262° and melts with decomposition at 275° C. (uncor.). Analysis proved that it contained two nitro groups.

0.1004 gram of substance gave 15.1 cc. of nitrogen at 744 mm. and 21° C.

	Calculated for $C_{16}H_{12}N_4O_5$. Per cent.	Found. Per cent.
Nitrogen	16.47	16.75

Nitration in the Presence of Mercury.

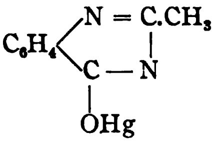
According to the patent D. R. P. 214,045[32] an hydroxyl group can be introduced besides a nitro group on the benzol nucleus of quinoline when nitration is carried out in presence of mercury.

15 cc. of fuming nitric acid were added to some mercury and while action was taking place 2 grams of the 2-methyl-4-quinazolone were introduced. On boiling off the excess a brown to black mixture was obtained which poured into water, gave a bright yellow precipitate.

This substance was insoluble in dilute alkalis, alcohol, potash, ethyl alcohol, benzol, aniline, nitrobenzol, ether, chloroform, toluene, amyl acetate, and isoamyl alcohol. It was soluble in glacial acetic acid and mineral acids from which it could be precipitated as a gelatinous mass by alkalis. From hot glacial acetic it separated as a bright yellow powder.

Indications pointed to a mercury salt. A portion was dissolved in aqua regia the excess of acid evaporated and diluted with water. Hydrogen sulphide gave a black precipitate which proved to be mercury.

A nitrogen determination gave good results for



.—This compound was not investigated further.

0.1014 gram of substance gave 7.1 cc. of nitrogen at 749 mm. and 21° C.

	Calculated for $C_9H_7N_2OHg$. Per cent.	Found. Per cent.
Nitrogen	7.79	7.85

Bromination of 4-Quinazolone and 2-Methyl-4-quinazolone.

All ordinary methods for bromination of these simpler quinazolones failed to give any results. Recourse was then had to Juvalta's[33] method.

In the first trial 2 grams of the quinazolone were added to 60 cc. of fuming sulphuric acid and then 2 cc. of bromine were added to this mixture. The flask was connected to a reflux condenser and the mixture gradually heated to 190° C. At that temperature white fumes mixed with bromine vapors were emitted from the top of the condenser so that the temperature was not carried any higher. After cooling the reaction mixture was neutralized carefully with dry sodium carbonate until only a slight acidity remained. This was poured into water and a dark brown precipitate fell. In case of the 2-methyl-4-quinazolone part of the precipitate was soluble in ethyl alcohol and gave a melting point of 327° C. (cor.). It could be dissolved in dilute potassium hydroxide from which it was precipitated as a colloidal gelatinous mass by acetic acid. Analysis failed to give any clue to its composition. The precipitate obtained from 4-quinazolone was insoluble in ethyl alcohol and dilute caustic potash. It was soluble in alcoholic potash from which it could be obtained by precipitation with acetic acid. It melted above 360° C. Analysis failed to identify the product. Both compounds were of a grayish color and contained considerable bromine.

Monobrom-4-quinazolone.

On a subsequent trial using the same quantities as above, the temperature was kept at 115° C. for one and a half hours instead of at 190° C. After neutralizing and pouring into 300 cc. of cold water, a heavy, dark brown precipitate fell. This was filtered, dissolved in hot dilute ethyl alcohol and boneblacked. From the filtrate a whitish flocculent mass separated and more was recovered from the boneblack by treating with hot alcohol, although considerable was lost during the process. It could be further purified by dissolving in dilute caustic potash and reprecipitating with acetic acid. The substance was soluble in hot acetone, methyl and ethyl alcohols; insoluble in hot water, benzol, ether and chloroform. The melting point was 258° C. (uncor.). Analyses proved it be a monobrom derivative.

0.1012 gram of substance gave 11 cc. of nitrogen at 762 mm. and 23° C.

0.1600 gram of substance gave 0.1346 gram of silver bromide.

	Calculated for $C_8H_5N_2OBr$. Per cent.	Found. Per cent.
Nitrogen	12.44	12.28
Bromine	35.55	35.79

Monobrom-2-methyl-4-quinazolone.

The details were conducted as above. The precipitate was soluble in dilute caustic potash and came down gelatinous on precipitating by acetic acid. The final product was of a grayish color and melted at 277° C. (uncor.). It was insoluble in hot benzol and ether; partly soluble in cold methyl alcohol and hot acetone.

0.1029 gram of substance gave 10.8 cc. of nitrogen at 754 mm. and 23°.

0.1507 gram of substance gave 0.1204 gram of silver bromide.

	Calculated for $C_9H_7N_2OBr$. Per cent.	Found. Per cent.
Nitrogen	11.71	11.73
Bromine	33.47	33.99

RESUME.

1. 3-Ethyl and 3-benzyl-4-quinazolone were prepared by alkylation.

2. 2-Methyl-3-*p*-nitrophenyl and 3-methyl-3-*p*-tolyl-4-quinazolones were obtained by condensing *p*-nitraniline and *p*-toluidine, respectively, with acetanthranil. In the same way 2-methyl-3-α- and 3-β-naphthyl-4-quinazolones were prepared from the naphthylamines.

3. The quinazolones will add alkyl iodides only under pressure and moderate temperature (110° C.).

4. It appears certain that the alkyl iodide adds to position 1, otherwise the same product would result from addition of methyl iodide to 2-methyl-3-ethyl-4-quinazolone as from addition of ethyl iodide to 2-methyl-3-methyl-4-quinazolone; *i. e.*, if the addition had occurred on position 3; however, different substances were obtained.

5. The iodethylates were invariably more soluble in methyl alcohol and water than the iodmethylates.

6. When heated with methyl iodide, 4-methoxyquinazoline, 4-quinazolone, and 3-methyl-4-quinazolone give one and the same product.

7. Generally the addition products melted with evolution of gas. The exceptions noted belonged to those compounds which contained only the imino group in position 3, *i. e.*, 2-methyl-4-quinazolone and 2-styryl-4-quinazolone, etc., melt quietly.

8. Of the nitroquinazolones tried, only the 6-nitro-3-methyl-4-quinazolone added methyl iodide and this appeared to give an intermediate product before the iodmethylate itself was obtained.

9. It was found much harder to add ethyl iodide to the styryl quinazolones than methyl iodide.

10. When the styryl quinazolones contained a phenyl, naphthyl, anisyl, or phenetyl radicle in position 3, they would not add methyl iodide at 150° C. and ten hours heating. A tolyl radicle in 3, however, did not interfere but yielded a splendid product.

11. If the iodmethylates of the 2-methyl-3-R-4-quinazolones were heated with silver salts, no products could be isolated.

12. When 2-styryl-4-quinazolone and 2-*m*-methoxy-*p*-oxystyryl-4-quinazolone iodmethylates were treated with silver nitrate, the methyl nitrate addition product resulted. However, when silver oxide, sulphate and acetate and sodium alcoholate acted on the 2-styryl-4-quinazolone iodmethylate

the product obtained in each case was the same and apparently it did not contain an hydroxyl group.

13. When 1-(4quinazolonyl)-4-phenyl-1,3-butydiene iodmethylate was treated with silver nitrate, the methyl nitrate addition did not form, but it appeared that the compound resulting was analogous to that obtained by the action of silver oxide, sulphate, etc., on the 2-styryl-4-quinazolone iodmethylate.

14. Nitration of the quinazolones requires high temperature and a dehydrating agent to accomplish the reaction.

15. The simpler nitroquinazolones can be reduced with stannous chloride and hydrochloric acid, but the yield obtained was poor, the reason not being perfectly clear.

16. On nitration of the quinazolones which contained no aryl radicle in position 3, the entering nitro group takes position 6.

17. When there is an aryl radicle in position 3, such the phenyl and *p*-tolyl radicle, two nitro groups enter on nitration.

18. The position of a nitro group in the *p*-position on the aryl radicle, allows the entrance of only one nitro group.

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BIOGRAPHY.

George Augustus Geiger was born in Orange, New Jersey, on August 24, 1886. In the fall of 1904, he entered Harvard College from which he was graduated in 1908 with the degree of Bachelor of Arts in Chemistry. During the academic year 1908–'09, he pursued a graduate course in the Analysis of Foods and Drugs at the New York College of Pharmacy. In September, 1909, he matriculated in Columbia University as a candidate for the higher degrees, and in June, 1910, received the degree of Master of Arts. During the Summer Session of 1910, he continued his studies at Columbia and in the fall returned as a candidate for the degree of Doctor of Philosophy, having been appointed University Scholar in Organic Chemistry.

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